



ORIGINAL STUDIES

Initial experiences with a novel biodegradable device for percutaneous closure of atrial septal defects: From preclinical study to first-in-human experience

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Abstract

Objective: To evaluate the feasibility, safety, and effectiveness of a novel, absorbable atrial septal defect (ASD) closure device made of poly-L-lactic acid (PLLA) in a swine model of ASD and for the first time in humans.

Methods: A preclinical safety study was conducted using a swine model of ASD. In a clinical setting, five pediatric patients underwent ASD closure with the PLLA device with fluoroscopic and transthoracic echocardiography guidance. The procedural results and clinical outcomes at 1 day, 30 days, 3 months, and 6 months after closure were analyzed.

Results: The 24- and 36-month follow-up results of the preclinical study demonstrated that the PLLA device exhibited good endothelialization and degradability in the swine model. In the clinical study, successful device implantation was achieved in all five patients (median age, 3.6 years; range, 3.1–6.5 years). The mean defect size was (13.6 ± 2.7) mm. Follow-up at 30 days, 3 months, and 6 months was completed in all five cases. The complete defect closure rates with no residual shunt at 30 days, 3 months, and 6 months follow-up were 60% (3/5), 80% (4/5), and 80% (4/5), respectively. No device dislodgement, significant aortic valve or mitral valve regurgitation, new onset cardiac arrhythmia, or other adverse events were reported.

Conclusion: The study results demonstrated that it is feasible to implant the PLLA device for closure of small to medium sized ASDs without significant residual shunts or severe adverse events in humans. The PLLA device exhibited good endothelialization and degradability in the swine model at 24 and 36 months. Further studies to evaluate long-term safety and effectiveness with the device in a large cohort of patients are warranted.

KEYWORDS

absorbable implants, catheterization closure, congenital heart defect, device

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1 | INTRODUCTION

An atrial septal defect (ASD) is a common cardiac congenital anomaly accounting for about 30% of cases of congenital heart disease. With the development of interventions and cardiac catheterization, percutaneous closure has become the first-line therapy for ASD patients. To date, all available devices for interventional closure of an ASD in humans are made of permanent materials. Among them, nickel-titanium-alloy occluders are most widely used. However, various early and long-term complications with the use of a device for ASD closure have been reported, which include erosion or perforation of the device, severe valvular damage, delayed endothelialization, thrombus formation, atrial arrhythmia, nickel allergy, and infective endocarditis.¹⁻⁷ Furthermore, permanent devices obstruct trans-septal access for future procedures of acquired heart disease. Therefore, there is a clinical need for the development of bioresorbable implants to reduce possible long-term complications.

The successful development of the BioSTAR bioresorbable patent foramen ovale (PFO) closure device (NMT Medical, Boston, MA) along with the encouraging results of the 6-month BioSTAR Evaluation Study^{8,9} represent a huge step forward from the use of metal to biodegradable occlusion devices. Besides the BioSTAR septal occluder, other partially biodegradable devices have also been developed, including the Biodisk and Double Biodisc devices.^{8,10,11} The BioSTAR device was the first partially bioresorbable occluder approved for ASD and PFO closure in humans.^{9,12,13} It consists of a metallic permanent double-umbrella framework (MP35N) and a bioresorbable membrane made from acellular porcine intestinal collagen.⁹ Early and late complications reported in clinical studies were considered to be attributable to the biological material and immunological properties of the device.¹⁴ Although the BioSTAR device was withdrawn from the market, it has inspired new ideas for the future development of biodegradable devices.

The use of completely bioresorbable septal defect occlusion devices in an experimental setting has been reported, including the "Chinese lantern" device, which is made of fully biodegradable polymers,¹⁵ the polydioxanone/poly (L-lactic acid) (PLLA)¹⁶ device, the PLLA/poly (D, L-lactic acid) (PDLLA)¹⁷ device, and the Carag bioresorbable septal occluder (Carag AG, Baar, Switzerland), which

consists of a framework made of a poly(lactic-co-glycolic acid) monofilament.¹⁸ In addition, Liu et al¹⁹ introduced a novel biodegradable occlusion device made of poly(ϵ -caprolactone) (PCL) and poly-D-L-lactide-glycolide (PLGA)/collagen nanofibers. *in vitro* studies have shown that the PCL device with a PLGA/collagen nanofibrous membrane had comparable mechanical properties to that of commercial metallic occluders. Although the effectiveness and safety of these new devices have been confirmed in animal models, the feasibility and safety in humans remain to be determined.

The 12-month outcomes of our previous preclinical studies demonstrated that the implanted PLLA biodegradable device achieved good endothelialization and degradability in short and moderate term follow-ups in a swine model of ASD.^{20,21}

In the present article, we report the 24- and 36-month follow-up results of PLLA device implantation in an animal model and describe the first human experience with the PLLA device for ASD closure in a consecutive series of patients by focusing on the feasibility and preliminary efficacy at 6 months.

2 | METHODS AND MATERIALS

2.1 | Device description

The PLLA device is a biodegradable ASD closure device with a self-expandable, double-disc framework made of 0.006-in. (0.15 mm) PLLA wire meshes (Figure 1). PLLA membranes are sewn onto the two discs and the waist with PLLA sutures. The PLLA device has seven platinum-iridium radio-opaque marks, with one at the tip of the left atrial disc, two at both ends of the discs, and two at the waist (Figure 2). A locking system, which is composed of a PLLA stick, is attached to the left disk on one side and coaptated to the delivery system with an angle tip and internal screw on the other. By controlling the locking system, the device can be in the "unlocked" or "locked" state (Figures 1 and 2). The details of the device structure are described in our previous preclinical study.²¹ The device is available in various sizes ranging from 6 to 32 mm at 2-mm increments.

The delivery system consists of a delivery cable, a handle, a loader, an assistant loader, and a hemostatic valve (Figure 3a). The controlling portion of the handle consists of a locking wheel, a push button, and a

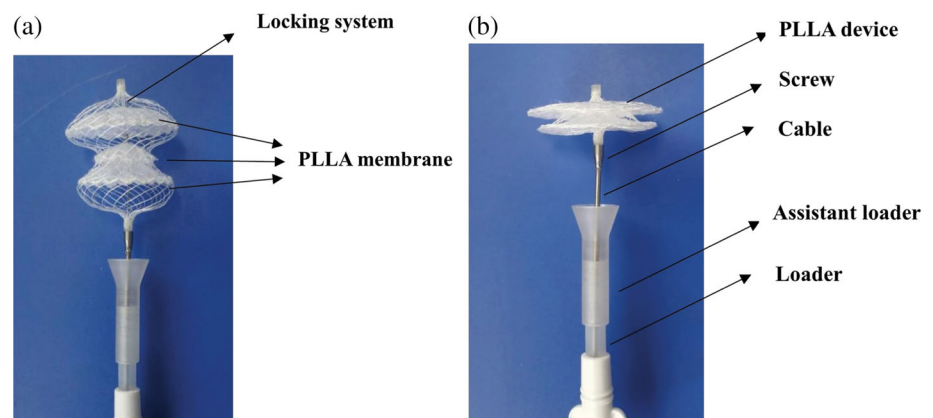


FIGURE 1 The double-disc structure of the PLLA device. (a) Unlocked state; (b) locked state [Color figure can be viewed at wileyonlinelibrary.com]

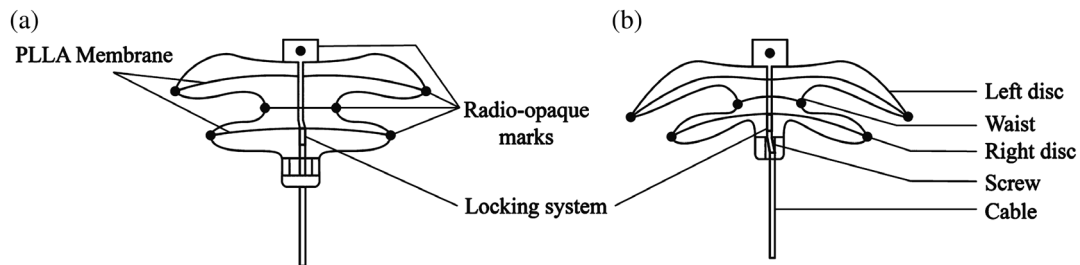


FIGURE 2 Schematic drawing of the PLLA device. The seven platinum-iridium radio-opaque marks are shown. (a) Unlocked state. (b) Locked state

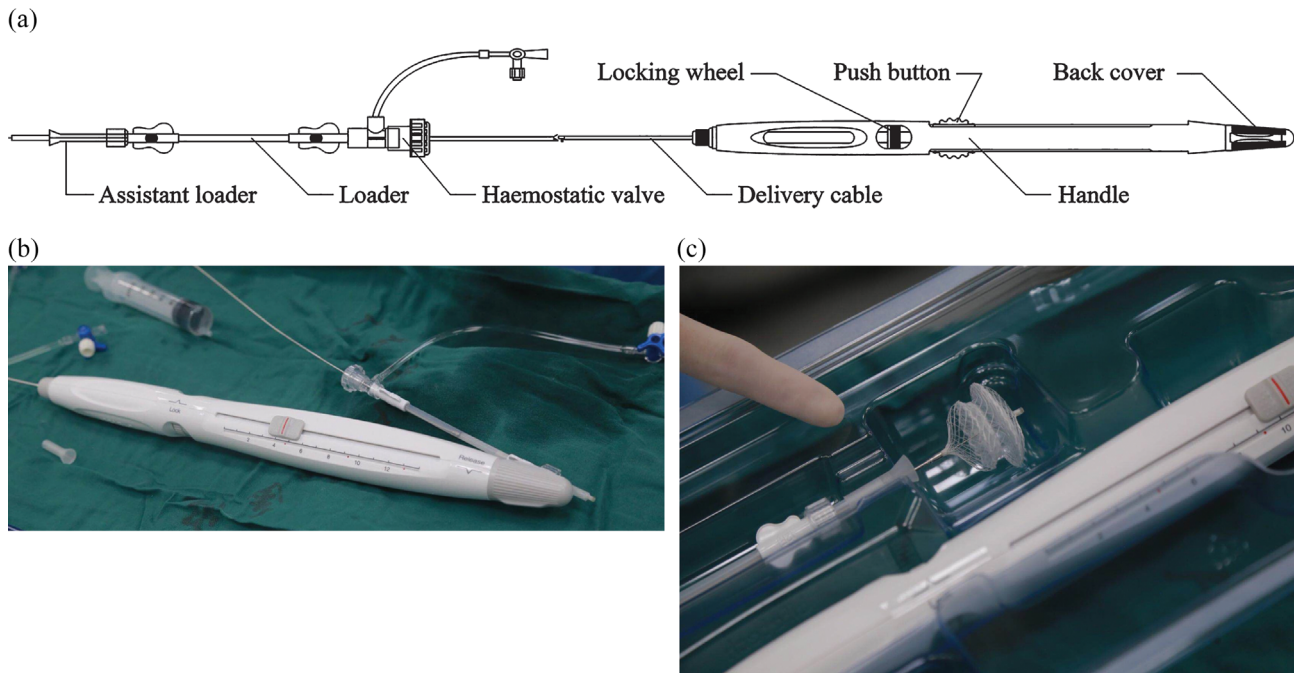


FIGURE 3 The PLLA device and the delivery system. (a) The delivery system. (b) The controlling portion of the handle. (c) The PLLA device is preloaded with the delivery system [Color figure can be viewed at wileyonlinelibrary.com]

back cover (Figure 3b). The handle enables deployment, locking of the preloaded device via the locking wheel, and repositioning and retrieval of the device via the push button. There are three marks on the handle as indicators to identify the position of the push button during device deployment, with one at the starting point, one at the mid position, and one at the end. Before device deployment, the back cover is pulled back and more than 10 counterclockwise rotations are made, followed by counterclockwise rotations of the controlling handle to disconnect the delivery cable from the screw of the device.

The PLLA device is preloaded with the delivery system (Figure 3c) and rehydrated with saline solution before loading into the loader.

2.2 | Preclinical study

Between October 2013 and March 2017, a total of 63 experimental piglets, consisting of both males and females (weight, 21–30 kg; age, 8–10 months old), were used in the study. Preoperative clinical

examination and transthoracic echocardiography (TTE) demonstrated that all of the piglets were healthy with morphologically normal hearts. The piglets were obtained from the Gateway Medical Innovation Center (Shanghai, China) and Mingzhu Experimental Animal Scientific Technology Company (DongGuan, Guangdong, China). The study protocol was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences. The housing facility met the guidelines of Laboratory Animal Requirements of Environment and Housing Facilities (GB 14925-2001). The care of laboratory animals and experimental surgery conformed to the guidelines of the "Chinese Administration Rules for the Care of Laboratory Animals."

PLLA devices were implanted into 45 piglets (mean weight, 26.3 kg) as the experimental group, while the other 18 piglets (mean weight, 27.9 kg) were implanted with Heart™ nitinol ASD devices (Lifetech Scientific, Shenzhen, China) as the control group. The methods used for percutaneous transcatheterization and ASD closure are described in our previous study.²⁰

The animals were followed-up at 1, 3, 6, 12, 24, and 36 months after device implantation. Chest X-ray, TTE, electrocardiography (ECG), and blood tests were performed periodically. Two or three animals from each group were sacrificed at different time points and the hearts, spleens, livers, lungs, and kidneys were removed for pathological examination. Gross anatomical examinations were performed to observe the morphologies of the device and adjacent anatomic structures. The harvested tissues from the implanted devices and atrial septum were subjected to histological analysis to evaluate the surrounding inflammatory response, endothelialization, and degradation of the PLLA wires and membrane. Moreover, scanning electron microscopy and immunohistochemical analysis were selectively performed to observe the process of endothelialization.

3 | CLINICAL STUDY

3.1 | Patients and ethical approval

Between May and June 2018, five pediatric patients (four boys and one girl) who were scheduled for percutaneous closure of secundum ASD at our hospital were included in the study. The diagnosis and evaluation of ASD prior to closure was performed by TTE for all patients. Indications for ASD closure were: an ASD ≥ 5 mm and ≤ 30 mm in diameter, with sufficient rims of atrial tissue (superior to the coronary sinus, superior/inferior vena cava, and pulmonary vein by 5 mm and superior to the mitral valve by 7 mm), signs of right ventricular volume overload and/or evidence of significant left-to-right shunting ($Q_p:Q_s \geq 1.5:1$). Patients with other congenital or significant cardiac defects, history of ASD repair, or previous left atrial appendage occlusion were excluded from the study.

The study protocol was approved by the Institutional Review Board of our hospital and conducted in accordance with the Declaration of Helsinki. Written informed was obtained from the parents or legal guardians of all patients prior to study participation.

3.2 | Device implantation procedure

The closure procedure was performed with fluoroscopic and TTE guidance under general anesthesia. A prophylactic antibiotic (cefazolin) was administered prior to device implantation. Intravenous heparin (100 IU/kg) was administered to achieve an activated clotting time of >250 s. Femoral venous access was obtained for diagnostic cardiac catheterization. A 0.035-in. J-tip wire was placed in the left upper pulmonary vein (LUPV) through the ASD and was exchanged for a 0.035-in. extra stiff guidewire using a 6-Fr multipurpose catheter. The maximal diameter of the defect was determined by TTE in multiple planes during the procedure (Figure 4a–c). The device size (waist diameter) was chosen by the interventional cardiologist based on the results of TTE measurements. A PLLA device 4–6 mm larger than the defect size was selected to close the defect, according to the common view of Chinese medical experts on interventional treatment of ASD.²² For defects with sufficient rims, a device 4 mm larger than the defect size was chosen, while for those with floppy rims or within

a floppy interatrial septum, a device 6 mm larger than the defect size was chosen. A delivery sheath (10F to 12F) was positioned into the LUPV. After rehydration with saline solution, the PLLA device was pulled into the loader and fixed in the “locked” state. The loader was introduced into the delivery sheath and the PLLA device was advanced into the LUPV (Figure 4d). Delivery of the PLLA device was similar to that previously described for the Amplatzer ASD device.²³ The delivery sheath was retracted until the whole device was exposed from within the sheath (Figure 4e). Under both fluoroscopic and TTE guidance, the device was unlocked, and the left atrial disc, the waist, and part of the right atrial disc were opened using the push button on the handle. The location of the device was appropriately adjusted to ensure the left atrial disk was located at the left side of the atrial septum (Figure 4f,g). Under TTE guidance, the right atrial disk was fully opened (Figure 4h,i), while maintaining constant tension on the cable. With both discs located against the septum and the defect fully covered, the delivery system was activated to release the device (Figure 4j,k,l–n).

3.3 | Follow-up

On day 1 after device closure, TTE was performed to evaluate the device position, residual shunts, interference with adjacent structures, valvular function, and pericardial effusion. ECG was also recorded to evaluate cardiac arrhythmia. Follow-up data at 30 days, 3 months, and 6 months after device closure were obtained, including all events and symptoms, as well as the TTE and ECG results. All patients were prescribed aspirin (3–5 mg/kg once daily for 6 months) after closure.

The primary outcomes of interest were procedural success and residual shunts at follow-up, as well as the occurrence of major adverse events, such as sudden cardiac death, cardiac tamponade, device displacement or migration requiring cardiac surgery, cardiac erosion, thromboembolism, and air embolism. Secondary outcomes included new onset of cardiac arrhythmia, significant aortic valve or mitral valve regurgitation, and all-cause mortality.

3.4 | Statistical analysis

Continuous variables are presented as the mean \pm SD. Estimates of the occurrence of events are expressed as percentages. Data analysis was conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corporation, Armonk, NY).

4 | RESULTS

4.1 | Preclinical study

An ASD model was successfully created in 62 piglets. One animal died due to perforation of the inferior vena cava during ASD creation. Finally, 44 PLLA devices and 18 nitinol devices were successfully implanted into 62 piglets. The immediate procedural success rate was 100%.

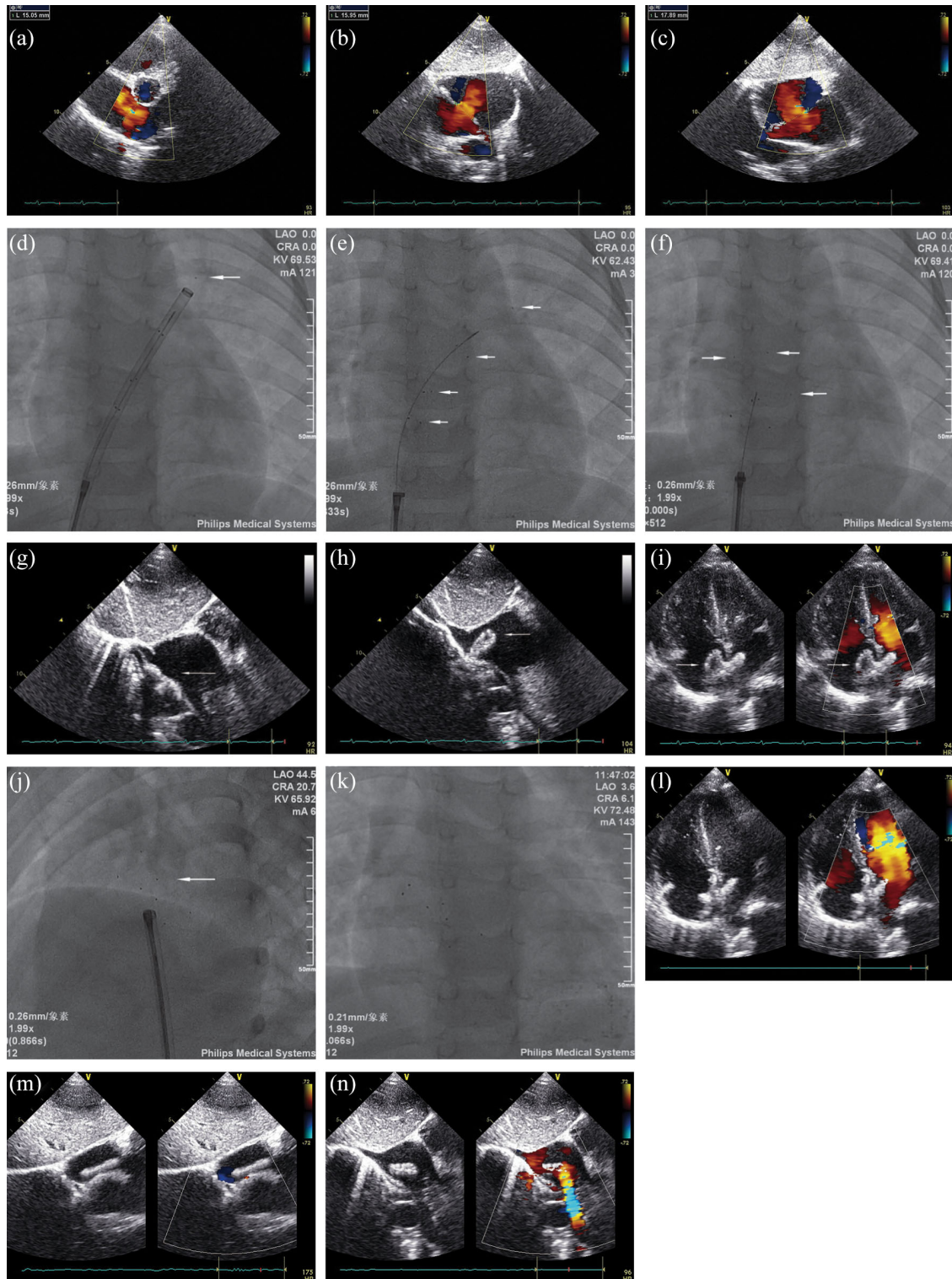


FIGURE 4 A case of percutaneous closure of ASD with the PLLA device. (a–c) The maximum defect size was 18 mm, as determined by TTE in multiple planes. (d) The PLLA device was advanced into the left atrium. Notice the seven radio-opaque marks under fluoroscopy. The white arrow shows the mark at the tip. (e) The left atrial disc, the waist, and the right atrial disc were exposed. White arrows indicated the seven marks. (f) The left disc was unfolded and positioned at the left side of the atrial septum. White arrows indicated the mark at the tip and two marks at the left disc. (g) The position of the left disc (white arrow) was monitored by TTE. (h) The right disc (white arrow) was unfolded under TTE guidance. (i) The shape and position of the device were observed at the apical four chamber view after the right disc was released (white arrow). (j) The positions of the seven marks (white arrow) under fluoroscopy upon device release. (k) The positions of the seven marks under fluoroscopy after device release. (l–n) TTE demonstrated the device was in good shape and positioned well [Color figure can be viewed at wileyonlinelibrary.com]

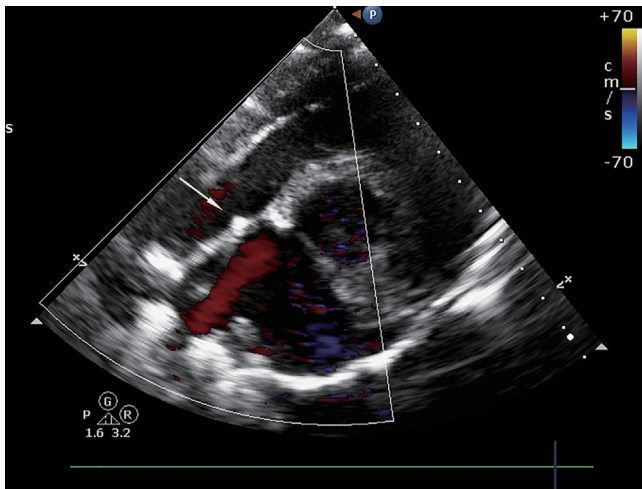


FIGURE 5 TTE evaluation at 24 months after device implantation in a swine model. The device (white arrow) was almost invisible [Color figure can be viewed at wileyonlinelibrary.com]

A total of 48 piglets, including 30 from the experimental group and 18 from the control group, were sacrificed at 1, 3, 6, and 12 months of follow-up. TTE and macroscopic studies demonstrated that both devices exhibited good occluding effects at each follow-up, with no device dislodgement, atrioventricular valve insufficiency, or thrombus formation. At the 3-month follow-up, the PLLA devices exhibited almost complete endothelialization, which appeared to be more sufficient, as compared to the control group. At the 12-month follow-up, histological analysis showed that the PLLA devices were partially degraded, with a number of collagen fibers, fibroblasts, and inflammatory cells surrounding the device. The macroscopic studies at the same time showed that the PLLA devices were still in a stable formation with no loss of integrity at the atrial septum. Details of the follow-up results are reported in our previous studies.^{20,21}

At the 24-month follow-up, TTE demonstrated that the PLLA device was almost invisible (Figure 5). No residual shunts or significant aortic or mitral valve regurgitation were noted. Macroscopic

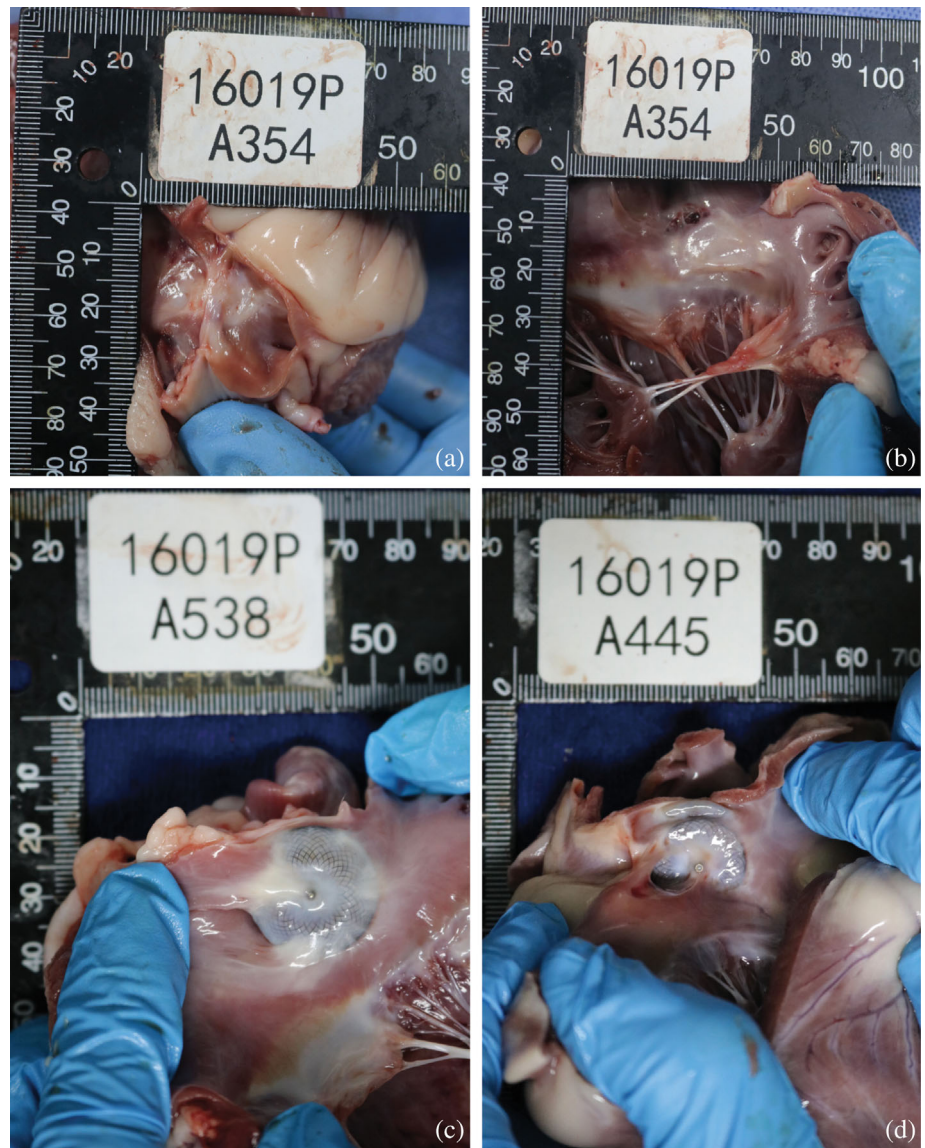


FIGURE 6 Macroscopic examination of the PLLA device and nitinol device at 24 months. (a) The left disc of PLLA device was fully covered by new endothelial tissue. (b) The right disc of the PLLA device. (c, d) The metal wires at both discs of the nitinol device were still visible [Color figure can be viewed at wileyonlinelibrary.com]

examinations showed that the PLLA device was not identifiable and became an integral part of the septum. Both discs had been totally covered by new endothelial tissue (Figure 6a,b). In contrast, although both discs of the nitinol device were covered by new endothelial tissue, the metal wires were still clearly visible (Figure 6c). Hematoxylin–eosin (HE) staining showed that most of the PLLA wires had disintegrated into pieces (Figure 7a). Large amounts of collagen fibers and fibroblasts were deposited around the PLLA device (Figure 7a,b). Chronic

inflammatory reactions consisted of a few lymphocytes that were loosely distributed in the newly formed tissue, but the inflammatory reactions were weaker as compared to that at the 12-month follow-up.

Similarly, at the 36-month follow-up, TTE demonstrated that the PLLA device was basically invisible, with no residual shunts, valvular insufficiency, or cardiac function impairment (Figure 8). Macroscopic examination showed that both discs of the PLLA device were completely substituted by autogenous tissue (Figure 9). HE staining

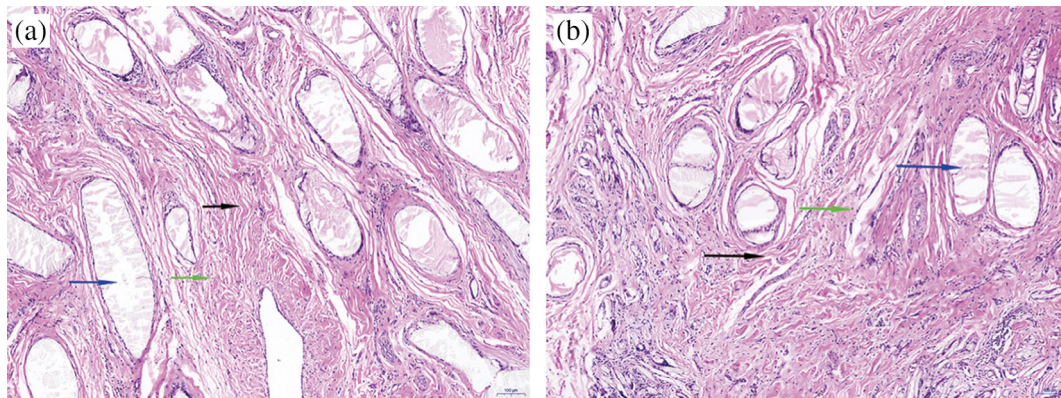


FIGURE 7 HE staining of the PLLA device at 24 months. (a, b) The PLLA pieces (blue arrow) were surrounded by large numbers of collagen fibers (black arrow) and fibroblasts (green arrow). A few inflammatory cells were observed in the newly formed tissue [Color figure can be viewed at wileyonlinelibrary.com]

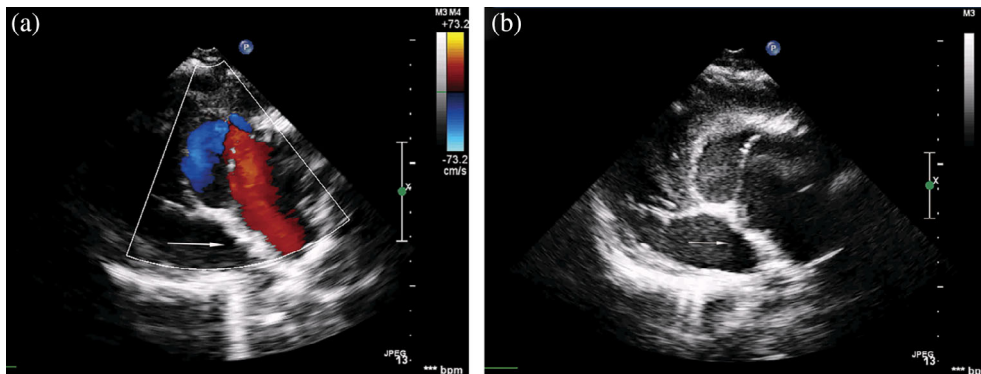


FIGURE 8 TTE evaluation at 36 months after device implantation in a swine model. (a) The device (white arrow) was fused with the atrial septum and no residual shunt was detected by TTE. (b) The device (white arrow) was basically invisible [Color figure can be viewed at wileyonlinelibrary.com]

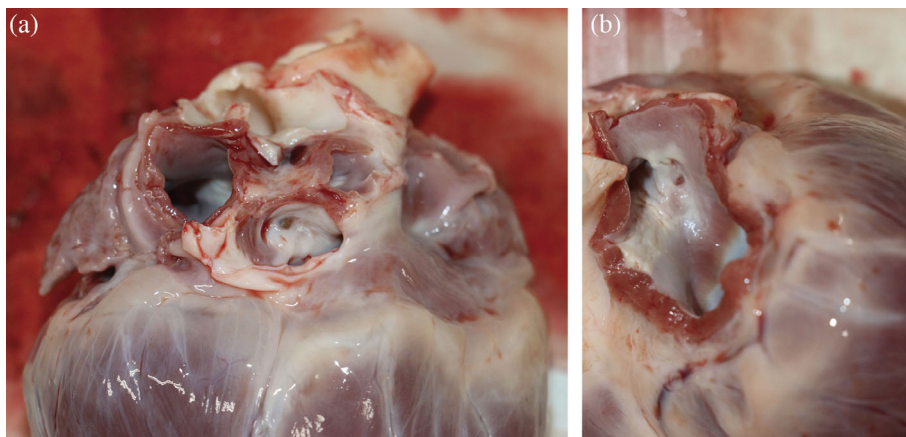


FIGURE 9 Macroscopic examination of the PLLA device at 36 months. (a, b) Both discs of the device were completely substituted by autogenous tissue and fused with the atrial septum [Color figure can be viewed at wileyonlinelibrary.com]

showed that there were no clear boundaries between the device skeleton and surrounding tissues, so Masson staining was used to identify the boundary between the new endothelial tissues and atrial septum (Figure 10a,b). The PLLA device was almost completely degraded, except for a small amount of PLLA from the tip of the device (Figure 10a). The skeleton of the device was replaced by a layer of thickened tissue that was composed of collagen fibers, fibroblasts, and newly formed vessels (Figure 10c,d). The presence of endothelial cells was confirmed by immunohistochemical staining of CD31 (Figure 10e). There was no evidence of significant inflammatory responses around the thickened tissues, necrosis, or tissue degeneration.

At the 24- and 36-month follow-ups, there were no abnormalities of gross specimens of the lungs, liver, spleen, and kidneys, with no evidence of thrombus formation or infarction.

4.2 | Clinical study

A total of five PLLA ASD closure devices were successfully and uneventfully implanted in all five patients. Patient characteristics are outlined in Table 1. The median age was 3.6 (range, 3.1–6.5) years. The mean body weight was 16.3 ± 5.7 (range, 10.0–23.5) kg. Right atrial and ventricular enlargement was observed in all five cases.

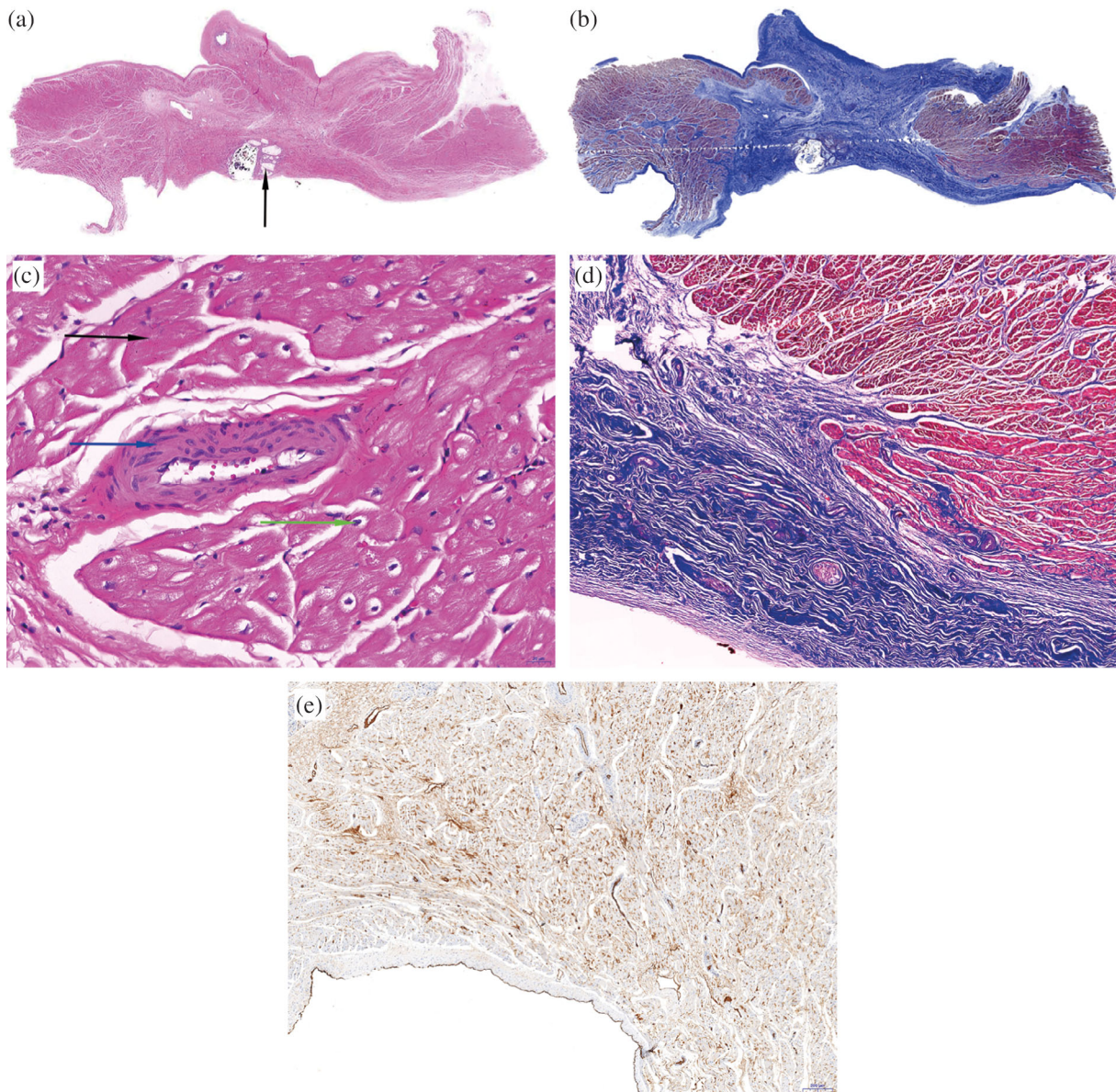


FIGURE 10 HE and Masson staining of the PLLA device at 36 months. (a) The boundary between the new endothelial tissues and atrial septum was not identifiable by HE staining. The arrow indicates a small amount of remaining PLLA at the tip. (b) Masson staining identified the boundary between the new endothelial tissues and atrial septum. (c) Large numbers of collagen fibers (black arrow), fibroblasts (green arrow), and newly formed vessels (blue arrow) were observed in the new endothelial tissues. (d) Masson staining showed a large amount of collagen fibers (in blue) in the new endothelial tissues. (e) Positive CD31 immunohistochemical staining confirmed the presence of endothelial tissues on the surface of device [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the five patients who underwent ASD closure procedure with PLLA device

Patient number	Age (years)	Weight (kg)	Gender	Recorded symptoms	Murmurs	Chamber dilation	Electrocardiography finding
1	4.9	23.5	Male	Asymptomatic	Systolic	RA and RV dilation	Normal
2	3.1	10.0	Male	Asymptomatic	Systolic	RA and RV dilation	Sinus tachycardia
3	6.5	21.0	Male	Asymptomatic	Systolic	RA and RV dilation	Normal
4	3.2	14.5	Female	Asymptomatic	Systolic	RA and RV dilation	Sinus tachycardia
5	3.6	12.5	Male	Asymptomatic	Systolic	RA and RV dilation	Normal

Abbreviations: RA, right atrium; RV, right ventricle.

TABLE 2 Procedure data of the five patients

Patient number	Defect size (mm)	Qp:Qs	Mean pulmonary pressure (mmHg)	Device size (mm)	Sheath (Fr)	Procedure time (min)	Fluoroscopy time (min)	Immediate residual shunt
1	17	1.7:1	22	24	12	52	7.6	None
2	14	2.0:1	19	20	12	26	5.4	None
3	15	1.8:1	22	20	12	31	6.0	None
4	12	1.5:1	13	18	10	44	7.3	None
5	10	1.5:1	17	14	10	28	5.5	None

Note: Qp:Qs: pulmonary-to-systemic blood flow ratio.

Procedural data are presented in Table 2. The mean ASD size was 13.6 ± 2.7 (range, 10–17) mm. The mean Qp:Qs ratio was 1.7 ± 0.2 :1 with a range of 1.5:1 to 2.0:1. The mean pulmonary pressure was 18.6 ± 3.8 mmHg. The mean procedural and fluoroscopy times were 36.2 ± 11.3 and 6.4 ± 1.0 min, respectively. There were no device retrievals or periprocedural complications. The immediate closure success rate was 100% (5/5).

On day 1 after device implantation, complete closure of the defect with no residual shunt was achieved in four (80%) of five cases (Table 3). No major adverse events, such as device dislodgement, thromboembolism, excessive pericardial effusion, or cardiac tamponade, were observed during or after implantation. New trivial mitral regurgitation was detected in three (60%) of the five cases. Sinus rhythm persisted in all of five cases on the day 1 after device implantation.

Follow-up data at 30 days, 3 months, and 6 months were obtained for all five patients (Table 3). No device dislodgement or significant aortic or mitral valve regurgitation were noted by TTE during the follow-up examinations (Figure 11). Trivial mitral regurgitation was detected in four (80%) of five cases at the 30-day follow-up, which disappeared spontaneously in all cases at the 3- and 6-month follow-ups. The rates of complete defect closure with no residual shunting at 30 days, 3 months, and 6 months were 60% (3/5), 80% (4/5), and 80% (4/5), respectively. Patient no. 1, who had a secundum ASD with a diameter of 17 mm and was implanted with a 24-mm PLLA device, exhibited a mild residual shunt at 30 days, which persisted at the 3- and 6-month follow-ups. While in the case of patient no. 4, a mild residual shunt was noted on day 1 after device closure and at the 30-day follow-up, but had resolved spontaneously at the 3- and

TABLE 3 Follow-up data of the five patients

	n	%
TTE at first day		
Device dislodgement	0	0
Thromboembolism	0	0
Residual shunt	1 (mild)	20
Aortic or mitral valve regurgitation	3 (trivial MVR)	60
TTE at 30 days		
Device dislodgement	0	0
Thromboembolism	0	0
Residual shunt	2 (mild)	40
Aortic or mitral valve regurgitation	4 (trivial MVR)	80
TTE at 3 months		
Device dislodgement	0	0
Thromboembolism	0	0
Residual shunt	1 (mild)	20
Aortic or mitral valve regurgitation	0	0
TTE at 6 months		
Device dislodgement	0	0
Thromboembolism	0	0
Residual shunt	1 (mild)	20
Aortic or mitral valve regurgitation	0	0
New onset cardiac arrhythmia	0	0
Death		
Cardiovascular death	0	0
Noncardiovascular death	0	0

Abbreviation: TTE, transcatheter thoracic echocardiography.

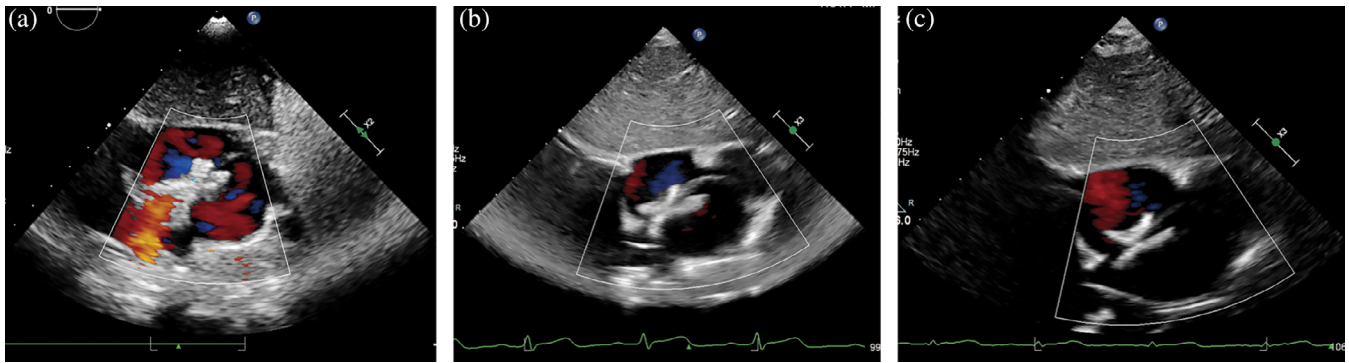


FIGURE 11 A case of TTE follow-up after 1 month (a), 3 months (b), and 6 months (c) after PLLA device implantation in humans. The device was in good shape and well positioned, with no residual shunts, aortic valve, or mitral valve regurgitation [Color figure can be viewed at wileyonlinelibrary.com]

6-month follow-ups. No new onset of cardiac arrhythmia or other adverse events were observed.

5 | DISCUSSION

To our knowledge, this is the first study describing the feasibility of a PLLA device for percutaneous ASD closure in humans. Our results confirmed the feasibility of transcatheter ASD closure with the use of a PLLA device. All procedures were performed successfully with no device- or procedure-related complication. The 6-month follow-up results demonstrated a high rate of shunt closure, with no residual shunts in four (80%) of five patients, as well as no severe regurgitation of the atrioventricular or aortic valves. No adverse events were noted during the follow-up study. Our preclinical study results showed good endothelialization with almost complete degradability of the PLLA device at 24 and 36 months. The results showed that the device had achieved long-term biocompatibility.

PLLA was used as the matrix of our biodegradable device. PLLA is a copolymer of PLA, which is reported to have high tensile strength, good flexibility, and good thermal stability.²⁴ Due to the biocompatibility and bioresorbability in the human body, PLA polymers have been used in a number of biomedical applications, including implants, drug delivery, and tissue engineering.^{25–27} After implantation of a PLLA device, endothelialization and degradability are two important factors in the healing process of an ASD. Recently, Lu et al¹⁷ reported the 2-year follow-up results of a biodegradable occluder in a sheep model of ASD, which consisted of a PLLA skeleton and two PDLLA discs. Complete endothelialization and disk absorption were observed at 12 months and there was a distinct decrease in the molecular weight of the framework (to 9% of the initial) at 24 months after implantation. Our previous studies showed that endothelialization started at 1 month after PLLA device implantation and was completed at 3 months in a swine model.²¹ Furthermore, the results of the present study demonstrated almost complete degradation of the PLLA device by 36 months with very few inflammatory responses.

Our first human clinical study demonstrated that the PLLA device could be safely and easily implanted for a small to medium sized ASD

with short procedural and fluoroscopic times. The delivery and deployment maneuvers of the PLLA device are easy and intuitive with the use of a simple handle control. The left disc is shaped by moving the push button to the mid-position on the handle. It is then maintained at the left side of the atrial septum and the right disc is shaped by moving the push button further distally. Recapture is easily accomplished by moving the push button in the opposite direction to retrieve the device into the delivery sheath. When the position is adequate, the push button is moved to the last mark at the end of the handle to complete right disc deployment. The device is then released from the locking piece by making counterclockwise rotations of the back cover on the handle. At this step, the device can still be retrieved with the locking piece reattached to the device by rotating the back cover in the clockwise direction. The device is finally released after detaching from the cable.

In this study, balloon sizing (stop-flow method) was not performed, since the procedure is relatively expensive and rarely used for percutaneous ASD closure in pediatric patients. According to the expert consensus in China, the absence of balloon sizing is not associated with an increased risk of technical failure of percutaneous closure of ASD in pediatric and adult populations. Based on our previous experience, the defect size could be clearly determined by TTE in multiple planes in pediatric patients with an excellent acoustic window. The reason for choosing a PLLA device 4–6 mm larger than the defect size was mainly based on the principle of metal device selection in the common view of Chinese medical experts regarding interventional ASD treatment.²² The results of the present study confirmed the feasibility of this method.

Our clinical study showed that one of the five patients (patient no. 1), with a 17-mm ASD and was implanted with a 24-mm PLLA device, exhibited a persistent mild residual shunt during follow-up, while our previous preclinical study results showed that no residual shunt was detected in the experimental group at 1, 3, 6, and 12-month follow-up.²¹ The difference between these results may due in part to the different natures of the defects. In a preclinical study, the defects were created by trans-septal puncture and balloon dilation with small sizes ranging from 4 to 7 mm and were centrally located

with good margins. A device 3–4 mm larger than the defect size was adequate to achieve complete closure. In a clinical study, larger defects ranging from 10 to 17 mm with floppy rims were included. In addition, during the first clinical procedures, there was a learning curve associated with the deployment technique and identifying the placement of the device under fluoroscopic and TTE guidance. Therefore, although we chose a device that was 7 mm larger than the defect size for patient no. 1, a mild residual shunt still existed, which was hemodynamically insignificant, thus no additional treatment was necessary.

The study results demonstrated some advantages of the PLLA device for closure of small to medium sized defects. First, the reduction in the number of PLLA wires (from 72 to 36) and the size of PLLA membrane makes it possible to deliver the PLLA device in a smaller sheath, which could be a huge benefit to pediatric patients. Second, the seven marks ensures visibility of the device by X-ray. Upon release, each group of the two marks at the left disc, the waist, and the right disc should be parallel, and the mark at the tip and two marks at the left disc should form a triangle. Any malformation or dislocation of the device could be detected by X-ray based on the location of the seven marks during and after the closure procedure. Third, the PLLA device is available in various sizes ranging from 6 to 32 mm at 2-mm increments, which permits its use for the treatment of a wide range of defect sizes from 5 to 28 mm. The PLLA device is greatly improved as compared to other biodegradable devices with configured sizes, such as the BioSTAR and Carag bioresorbable septal occluders, which have been used in clinical studies. Fourth, the PLLA device reserves the possibility of trans-septal puncture in future transcatheter procedures. In our preclinical study, fracture force was assessed with a tensile test with a strain rate of 10 mm/min in the newborn tissue group ($n = 3$) and the septum primum group ($n = 3$). There was no significant difference in the fracture force between the newborn tissue group and the septum primum group (11.07 ± 3.55 vs. 7.07 ± 1.84 N, respectively, $p = .181$), suggesting that the newborn tissue had similar biomechanical properties as the septum primum group, which makes future trans-septal puncture possible.

Compared to metal alloy occluders, the decreased fluoroscopic visibility of the PLLA device may lead to more difficult device retrieval with transcatheter techniques. In our preclinical study, a PLLA device (waist diameter, 20 mm) was intentionally implanted in the “unlocked state” and was embolized into the descending thoracic aorta. A 25-mm goose neck snare was applied to capture the waist of the device in the right femoral artery access. Another 15-mm goose neck snare was introduced to catch the tip of left disc to help stabilize the device in the left femoral artery access. The device was slenderized and pulled into a 14F sheath and successfully retrieved. However, no attempt has been made to retrieve a device in the “locked state” under fluoroscopic guidance. Based on our experience in vitro, it was harder to retrieve a device in the “locked state” into a same size delivery sheath, as compared to that in the “unlocked state.” Therefore, we suggest the use of a sheath larger than the initial delivery sheath to retrieve the embolized device. Moreover, since the marks on the device enable the identification of the position of the waist and the

tip of the left disc, the “Waist Capture Technique”²⁸ with a looped wire or a snare to capture the waist of the device might be feasible for device retrieval.

The PLLA device can achieve excellent results for a small to moderate sized secundum ASD (defect size 10–17 mm), although practical experience is lacking in patients with larger defects. Moreover, the endothelialization and degradation processes of the PLLA device in the human body remain unclear. Hence, further larger prospective clinical trials with long-term follow-up are needed to confirm these favorable preliminary results.

6 | STUDY LIMITATIONS

There were a few limitations to the present study. The major limitation was the very small cohort of patients from a single institution. Closure procedures using PLLA devices were performed for only small and moderate sized defects with sufficient rims. The patients were only followed for 6 months, thus the long-term safety of the PLLA device in humans remains unclear.

7 | CONCLUSIONS

The results of the present study demonstrated that it is feasible to implant a PLLA device in small to medium sized ASDs without significant residual shunts or severe adverse events in humans. Also, the PLLA device exhibited good endothelialization and degradability at 24- and 36-month follow-ups in a swine model. Studies to evaluate long-term safety and effectiveness of PLLA device in a larger cohort of patients are now warranted.

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