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Long-term bio-functional performance of a novel, self-positioning balloon expandable transcatheter biological aortic valve system in the ovine aortic banding model

Piotr P. Buszman[1, 2]*, Mateusz Kachel[1, 2]*, Krzysztof P. Milewski[1, 3], Magdalena Michalak[1], Wojciech Domaradzki[1], Maciej Pruski Jr[1], Michał Sobota[4], Carlos Fernandez[1], Karolina Łukasik[1], Jerzy Nożyński[5], Piotr Hirnle[6], Paweł Kaźmierczak[1], Andrzej Bochenek[1, 3], Paweł E. Buszman[1, 7]

[1]American Heart of Poland, Center for Cardiovascular Research and Development, Katowice, Poland
[2]Department of Cardiology, Andrzej Frycz Modrzewski Krakow University, Bielsko-Biala, Poland
[3]Faculty of Medicine, University of Technology, Katowice, Poland
[4]Polish Academy of Sciences, Center of Polymer and Carbon Materials, Zabrze, Poland
[5]Silesian Center for Heart Diseases, Zabrze, Poland
[6]Medical University of Bialystok, Poland
[7]Medical University of Silesia, Katowice, Poland

Abstract

Background: *The aim of the study was to evaluate bio-functionality of a novel, proprietary balloon-expandable biological transcatheter aortic valve implantation (TAVI) system (InFlow, CardValve Consortium, Poland) in an ovine model of aortic banding.*

Methods: *Surgical ascending aorta banding was created in 21 sheep. Two weeks later, 18 biological valves were implanted within the model using 15–16 F InFlow TAVI systems and carotid cut-down approach. Follow-up transthoracic echocardiography was performed at 30, 90, and 180-day. At designated time, animals were euthanized and valves harvested for analysis.*

Results: *All sheep survived the banding procedure. There were 4 (22%) procedure related deaths within a 7-day period. During the observation an additional 2 sheep died. In one, the valve dislocated after the procedure — the animal was excluded. Two animals completed 30-day follow up, five 90-day follow-up and four terminal follow-up of 180 days. Valves examined via transesophageal echocardiography showed proper hemodynamic parameters without evidence of structural valve deterioration. The maximum and average flow gradients at 180 days were 31.4 (23.3–37.7) and 17.5 (13.1–20.2) mmHg, respectively. There was one case of moderate insufficiency and no case of perivalvular leaks. By histopathology, there were no inflammation, thrombosis, nor calcifications in any tested valves at long-term follow-up. Neointimal coverage of stent struts increased with time from basal part in "early" groups to nearly 3/4 of stent length in the 180-day group. The pannus tissue showed maturation that increased with time with no stenotic "collar" visible in orthotopically implanted valves.*

Conclusions: *The study showed good hemodynamic performance, durability and biocompatibility of the novel biological transcatheter heart valve.* (Cardiol J 2024; 31, 1: 124–132)

Key words: aortic stenosis, transcatheter aortic valve implantation (TAVI), artificial heart valve, biological heart valve, preclinical study

Address for correspondence: Piotr P. Buszman, MD, PhD, Department of Cardiology, Andrzej Frycz Modrzewski Krakow University, Center for Cardiovascular Research and Development, American Heart of Poland, ul. Armii Krajowej 101, 43–309 Bielsko-Biała, Poland, tel: +48 32 758 65 14, e-mail: pbuszman@gmail.com

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**Both authors contributed equally.*

Introduction

The aortic valve stenosis treatment evolved drastically with the introduction of transcatheter aortic valve implantation by Cribier et al. [1] in 2002. The method itself was refined through recent decades resulting in expanding indications for transcatheter aortic valve implantation (TAVI) procedures as stated in both European and American cardiology guidelines [2, 3]. Performed studies have proved superiority of the method to medical therapy and surgery in prohibitive risk patients' group, with non-inferiority/superiority achieved in intermediate and recently in low-risk cohorts [4–8]. The above-mentioned facts facilitated the rapid growth of TAVI procedures performed worldwide with transcatheter intervention volume exceeding for the first time that of all forms of surgical aortic valve replacements in 2019 in the United States [9]. Still, the quotes remain insufficient when considering the need. In the European Union, the average number of TAVI per million inhabitants is around 140 (range 50–270), with an estimated need of around 250–300 procedures per million citizens performed annually [10]. Researchers showed that approximately 180,000 patients can be considered potential candidates for TAVI in the European Union and in North America, with a potential to increase up to 270,000 cases annually if indications were to expand further [10]. Furthermore, although latest data show very good long-term durability, with low percentage of structural valve degeneration, as the indications expand and TAVI valves are being implanted in younger patients, this may raise issues in the future [11]. Additionally, the remaining limitations of transcatheter procedures, such as paravalvular leak, myocardial injury, need for pacemaker implantation and vascular complications prompt are yet to be addressed. Therefore, there is a need for new technologies to be researched and developed to upgrade the method itself, as well as, to increase and endorse socially equal accessibility, especially in low-income countries or patient cohorts.

Presented herein, are short- and long-term results of a novel, proprietary biological transcatheter aortic valve prosthesis which was tested in a preclinical model of the aortic banding in an ovine.

Methods

Study design

The study protocol has been accepted by the Local Ethics Committee for animal research, Decision No. 150/2016. The Experiment was conducted in a GLP certified Center for Cardiovascular Research and Development of American Heart of Poland, Kostkowice, Poland. Twenty-one blackface crossbred sheep, approximately 2 years old, weighing 40 to 80 kg were included. Animals received an acclimation period of at least 21 days. All animals received standard of care outlined in the study protocol and in accordance with the act of animal welfare and the "Guide for the Care and Use of Laboratory Animals" [12].

The banding methods have been described and previously validated [13]. Briefly, ascending aorta delicate stenosis (AS) and anchoring mechanism was created by fixing a surgical band around the aorta. After AS creation, animals were allowed a recovery period of at least 10 days. Subsequently, Inflow™ transcatheter heart valve was implanted via carotid cut-down utilizing. Follow up echocardiography and complete blood works was performed at 30-, 90- and 180-day follow-up.

Study device

Inflow™ biological transcatheter heart valve was comprised of a balloon-expandable, radiopaque, cobalt-chrome alloy frame with a proprietary stent design, and a tri-leaflet, ultrathin swine pericardium valve connected with a cuff (Fig. 1). Biomaterials were attached to the metal frame using the standard suturing technique. The prosthesis is a terminally sterilized (using an antibiotic solution), single use device, indicated for relief of AS in patients with symptomatic heart diseases due to severe native calcified AS in patients at high or greater risk for open surgical valve replacement. For the study purpose Inflow™ transcatheter heart valve was available in a diameter equaling 23 mm and was used with dedicated, proprietary delivery system including self-positioning balloon shape and left ventricle protection system. After proper crimping the device outer diameter is 15–16 F. Devices are stored in an aldehyde solution. This transcatheter heart valve and delivery is covered with 5 international patents issued (no. P.426429, P.426432, P.426433, P.426434, P.426463).

Aortic banding model

Sheep were anesthetized using a combination of ketamine 10 mg/kg IM/IV + xylazine 0.05–0.2 mg/kg IM + atropine 0.1–0.2 mg/kg IM. Propofol 2–4 mg/kg IV was administered to facilitate intubation. Following successful intubation, sheep were placed in right lateral recumbency. Anesthesia was maintained using isoflurane (1–3% concentration).

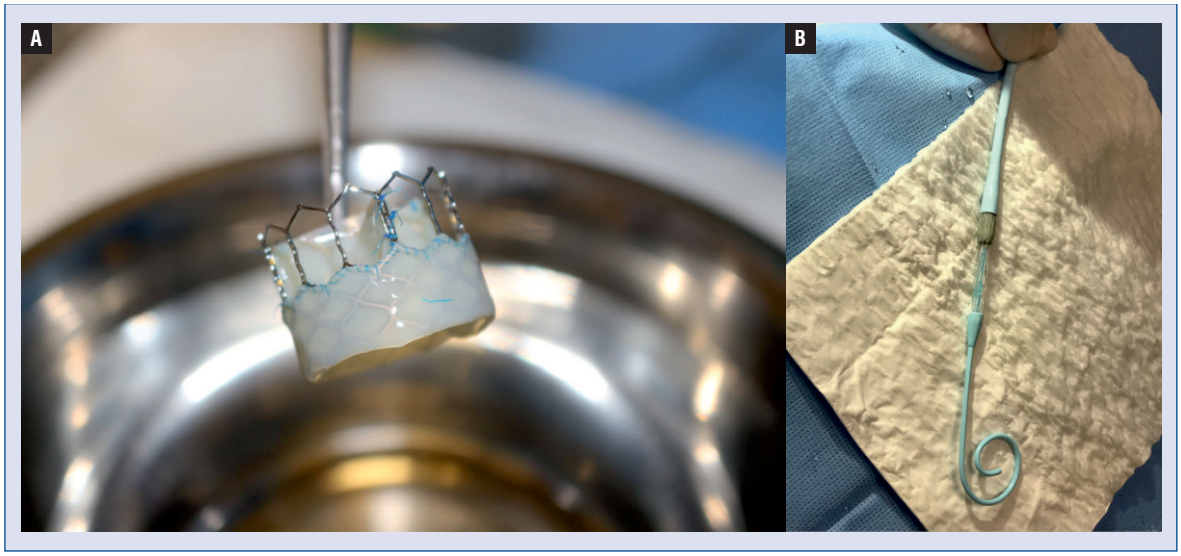

Figure 1. A. Biological Inflow heart valve prototype — lateral view; **B.** Inflow valve crimped on the balloon.

Additionally, continuous venous infusion of fentanyl was used to provide proper analgesia (0.003–0.006 mg/kg/h) during surgery. Aortic banding was achieved by means of a minimally invasive left side thoracotomy. An incision was made between the 4th and 5th intercostal space, and the ascending aorta was exposed. The target site for the banding implantation was mid-way from the native aortic valve and the common carotid trunk. With the help of sizer kits, the Dacron sleeve was measured, and the diameter of the aorta decreased between 2–4 mm. A surgical stainless-steel wire was sutured in the mid-line of the banding tissue to allow identification under fluoroscopy. After the procedure completion, the wound was closed, and the sheep moved to post-op recovery.

Transcatheter aortic valve implantation

Two weeks after the aortic banding, TAVI procedures were performed starting with anesthesia using the same procedures as outlined for the banding. Sheep were placed in dorsal recumbency with the legs stretched caudally. The left carotid artery was surgically exposed and prepared, as close to the thoracic inlet as possible. A 6 Fr arterial sheath was placed in the carotid artery. A J wire 0.035" was advanced through the arterial sheath in the left ventricle, and a 5 Fr pig-tail catheter with 10 mm markers was advanced over the J wire. A ventriculography and aortography along with invasive pressure evaluation were performed to assess the banding site and measure the target implantation site diameter. The pig-tail catheter markers were used to calibrate the distance. After all measurements were finished, the pig-tail catheter, and the J wire were removed. The valve was crimped on a balloon matching the valve size (a 23 mm balloon for a 23 mm valve), and the natural direction of blood flow from the heart (aortic position). The 6 Fr arterial sheath was removed and replaced with an arterial sheath bigger than the measured profile of the valve (usually 18–22 F). Once the large arterial sheath was inserted, heparin was administered at a dose of 300 IU/kg (3 mg/kg), IV, to achieve an activated clotting time over 300 s. A super stiff Amplatz wire was advanced through the arterial sheath into the left ventricle. The valve crimped on the balloon was advanced over the Amplatz wire and through the arterial sheath to the aortic banding. The valve was expanded with the help of a 50 mL syringe filed with 70:30 ratio of saline and contrast. Once the implantation was complete, the Amplatz wire, and the balloon were removed. Post implantation control ventriculography and aortography were performed as outlined above without changing the arterial sheath. The arterial sheath was removed, the carotid artery ligated, and the tissues and skin were sutured in three layers. The sheep was then transferred to post-op recovery. Post procedural anticoagulation regimen included daily administration of low molecular weight heparin (once daily, 1–2 mg/kg SC) for 30 days following intervention.

Echocardiography

Transthoracic echocardiography (TTE) was performed at 30, 90, and 180-day follow-up.

Transesophageal echocardiography (TEE) was performed at 180 days as a complement to TTE, while under anesthesia. All routine parameters were evaluated (left ventricle end-diastolic volume, aortic diameter, left ventricle end-systolic diameter, ejection fraction, cuspids separation, among others), and valve functionality, deployment, and any other visual findings were documented in the echo reports.

Pathological evaluation

The independent, pathology core lab (Silesian Center for Heart Diseases, Poland) received fixed, explanted hearts and ascending aorta for histopathology. Hearts were trimmed and the segment of tissue containing the explants was excised, grossly examined and radiographed. Aortic roots with valve implants were dehydrated in a graded series of ethanol, cleared in xylene, and infiltrated and embedded in SPURR plastic resin. After polymerization, the device with frame was sectioned radially twice to capture each cusp (left coronary cusp [LCC]; right coronary cusp [RCC]; non coronary cusp [NCC]) and stained with hematoxylin and eosin (H&E). In addition, the portion of the plastic block containing each of the three valve cusps (radial planes) was separated from the frame, cut serially twice (thin sections) and stained with Movat's pentachrome and Von Kossa. The block remnants were reassembled with appropriate spacers and cut crosswise (transverse plane) at two levels. All ground sections were ground and micro polished to optical finish using the Exakt cutting/grinding system. Resulting sections were stained with H&E. Trackable gross lesions submitted separately were processed, embedded in paraffin or SPURR resin as appropriate, sectioned and stained with H&E and/or Masson's trichrome (paraffin only). All resulting slides were evaluated via light microscopy by the study pathologist. In the event of identifying problems with valve function, the harvested tissues were then passed to the histopathology for analysis. If no correlation between reported death and valve function was revealed, further analysis was abandoned.

Statistical analysis

This is a prospective, observational and experimental study; therefore, no study hypothesis was made. Normally distributed data are presented as means and standard deviations, whereas non-parametric as proportions and percentage or medians and interquartile ranges. To test for temporal differences in echocardiographic parameters repeated measures ANOVA has been performed followed by the pairwise comparison with the Bonferoni modified paired T-test. A value of $p < 0.05$ was considered statistically significant. MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org) was used for analysis.

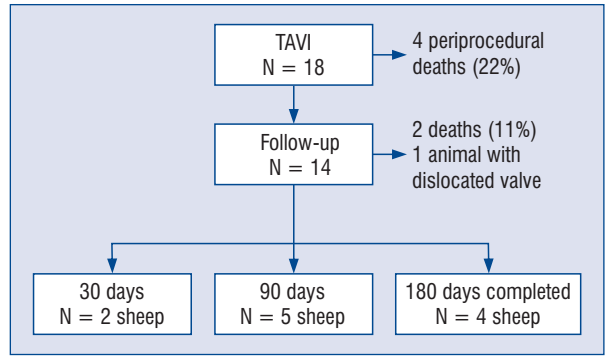

Figure 2. Study flowchart; TAVI — transcatheter aortic valve implantation.

Results

Surgical banding was performed in 21 sheep. All animals survived the banding-TAVI period. Out of these, 18 were assigned to the TAVI procedure. Three sheep were excluded due to the improper size of the banding location as reported in aortography. All valves were delivered successfully to the banding site and implanted. The aggregate periprocedural mortality (defined as up to 7 days after the procedure) amounted 4 (22%) animals. During the observation period an additional 2 sheep died. Complete observation was achieved in 11 animals, 2 for 30 days, 5 for 90 days and 4 for 180 days, respectively (Fig. 2). In 1 animal, that completed the 180 days observation, the implanted valve dislocated in the early days after the initial procedure and was later found anchored in the descending aorta, thus preventing the proper imaging and comparative histopathology evaluation — the animal was excluded from further analysis. The detailed mortality cause explanation is presented in Table 1.

Echocardiographic results

Echocardiographic analyses were conducted according to the protocol in respective time points of 30, 90 and 180 days. At the time of terminal control, TEE was utilized complementary to the standard transthoracic echo after previous induc-

Table 1. Mortality explained.

Cause of death	Number of animals
Sudden cardiac arrest — day 0, 9, procedural and anesthesia	2
Myocardial infarction — day 2, 7, low valve implantation	2
Stroke — day 7, high banding position, stenosis of common carotid trunk	1
Endocarditic and vegetations on prosthesis — day 63	1

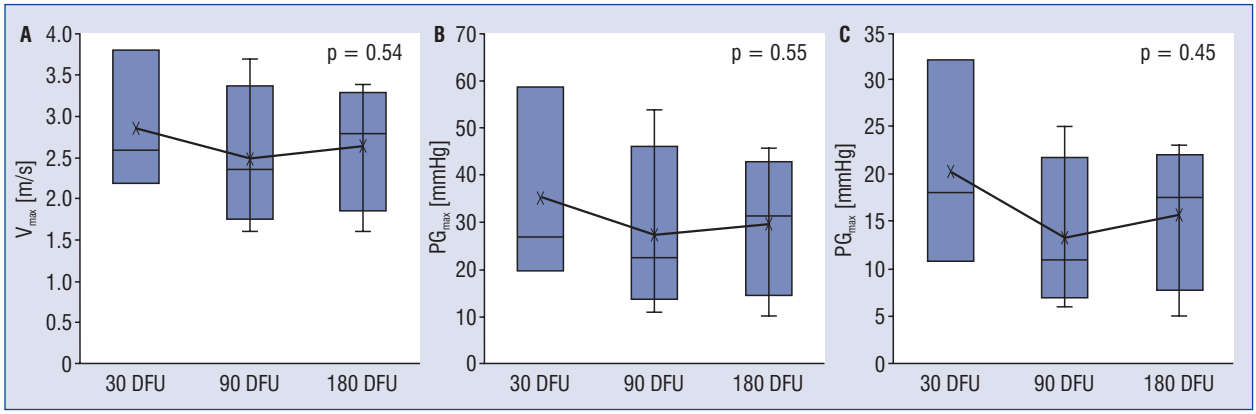

Figure 3. Maximal velocity (V_{max}) (**A**) and pressure gradients (PG_{max}, PG_{min}) (**B, C**) — serial measurements; DFU — days follow-up.

tion of anesthesia (at the time point of 30 and 90 days only TTE was performed). Imaging revealed consistent valve hemodynamics in respective time points, typical for percutaneously implanted prostheses (Fig. 3) There were no incidences of severe valvular insufficiency, with moderate grade regurgitation reported in 2 cases at 90 days and 1 at 180 days. No perivalvular leaks were observed. TEE revealed a probable vegetation present in 1 case at 30 days (confirmed in histopathology), and in 2 cases at 180 days (denied in histopathology). Detailed echocardiographic results are displayed in Table 2.

Histopathology

Necropsy evaluation encompassed 2 animals for 30 days, 5 animals for 90 days and 4 animals for 180 days. In the short-term observation group, the gross inspection showed in 1 case an intramyocardial abscess penetrating to the prosthetic element with subsequent bacterial vegetations. A second case evaluated showed elastic leaflets covered with endothelium, without any tears, fenestrations, or focal thickenings. Thin thrombi were visible as surface flat deposits. Radiogram showed punctiform linear calcifications inside leaflets. Histopathology revealed inflammatory infiltrations in periprosthetic and prosthetic tissues such as pannus and biological leaflet in both prostheses.

The mid-term group (90 days) pathology evaluation (5 cases) revealed thin elastic biological leaflets without any tears or fenestrations and with focal thickening of leaflets visible in 2 cases. In 1 case the leaflets were retracted with thickening of a free margin. Immature pannus was present only at the lower part of the stent. Neointima covered nearly 25% of leaflets and stent in 4 cases, with almost complete covering reported in 1 prosthesis. Small thrombi were reported in 2 valves. Detailed X-ray imaging displayed focal calcifications of free margin and commissures in 4 animals. No signs of inflammatory reaction were seen except for one animal, in which infiltration containing lymphocytes and histiocytes extended from pannus and covered the biological leaflet, and focally penetrated acellular leaflet tissue.

The 180-day group (4 cases) gross inspection showed thin elastic leaflets, without tears or fenestrations. Pannus was present only at stent. In 2 cases neointima covered only nearly 25% of leaflets and stent, nearly 50% in one and nearly

Table 2. Cumulative results of temporal transesophageal echocardiography and doppler evaluation.

Doppler measurements	30 DFU		90 DFU		180 DFU	
	Median	IQR	Median	IQR	Median	IQR
V_{max} [m/s]	2.6	2.5–3.2	2.3	1.94–2.73	2.8	2.4–3.1
PG_{max} [mmHg]	27.0	23.7–41.9	22.0	15–29.8	31.4	23.3–37.7
PG_{mean} [mmHg]	18.0	15.9–27.3	10.0	7.4–14.2	17.5	13.1–20.2
LVEDD	45.0	41–48	43.0	42–48	43	42.3–43
LVESD	27.5	25.8–30.5	29.0	29–31	28.5	27.5–30.5
ECHO findings	**N = 12**	**%**	**N = 9**	**%**	**N = 4**	**%**
Mild regurgitation	1	8.3	0	0	0	0
Moderate regurgitation	0	0	2	18.2	1	9.1
Possible calcification	0	0	0	0	1	9.1
Present calcification	1	8.3	1	9.1	1	9.1
Probable vegetation	1	8.3	0	0	2*	18.2
Mean PG > 30 mmHg	2	16.6	0	0	0	0

*Not confirmed in pathology; DFU — days follow-up; IQR — interquartile range; PG — pressure gradient; LVEDD — left ventricular end diastolic diameter; LVESD — left ventricular end systolic diameter

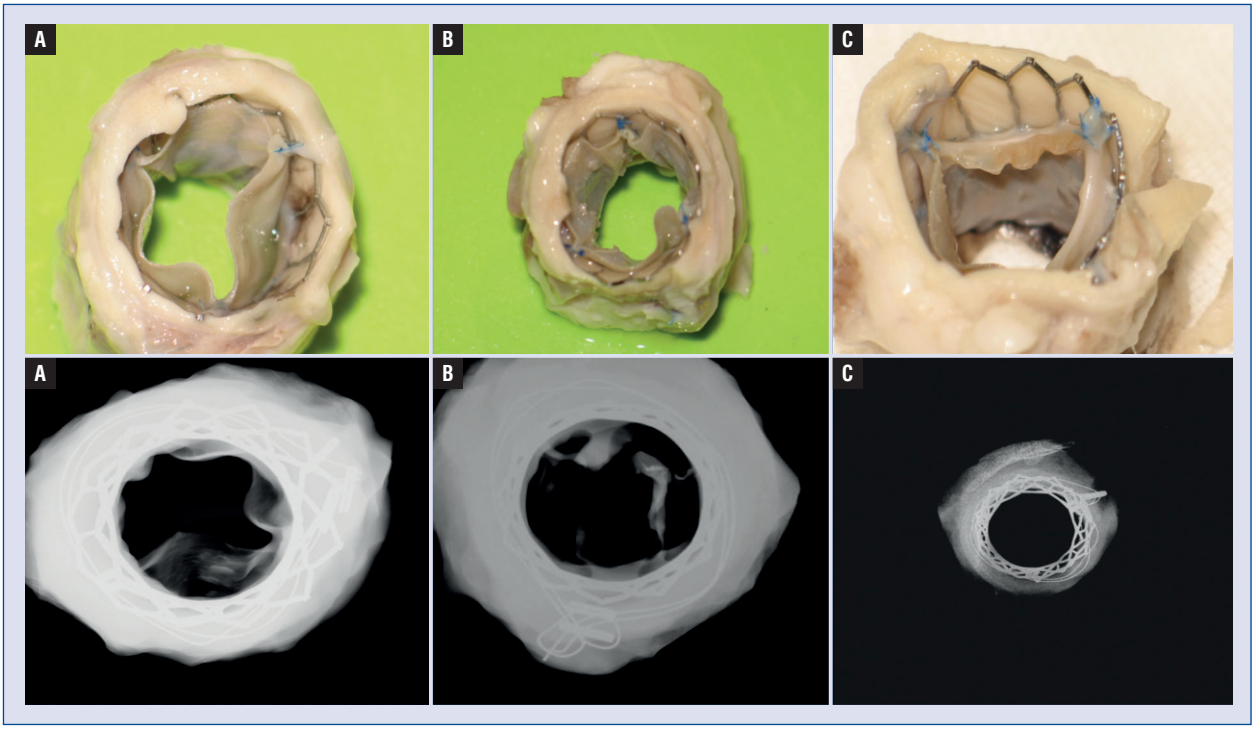

Figure 4. A–C. The representative images of explanted prostheses with radiograph and macroscopic inspection.

100% of both — leaflets in the remaining case. No thrombi were reported in any of the animals. Radiography did not find any symptoms of calcifications. Leaflets histopathology showed decellularized tissue covered by endothelial cells with no inflammatory infiltrations, whereas neointimal coverage contained dispersed mesenchymal cells and few lymphocytes (inflammation grade 0, endothelial grade 3/4). The representative images of explanted prostheses are displayed in Figures 4 and 5.

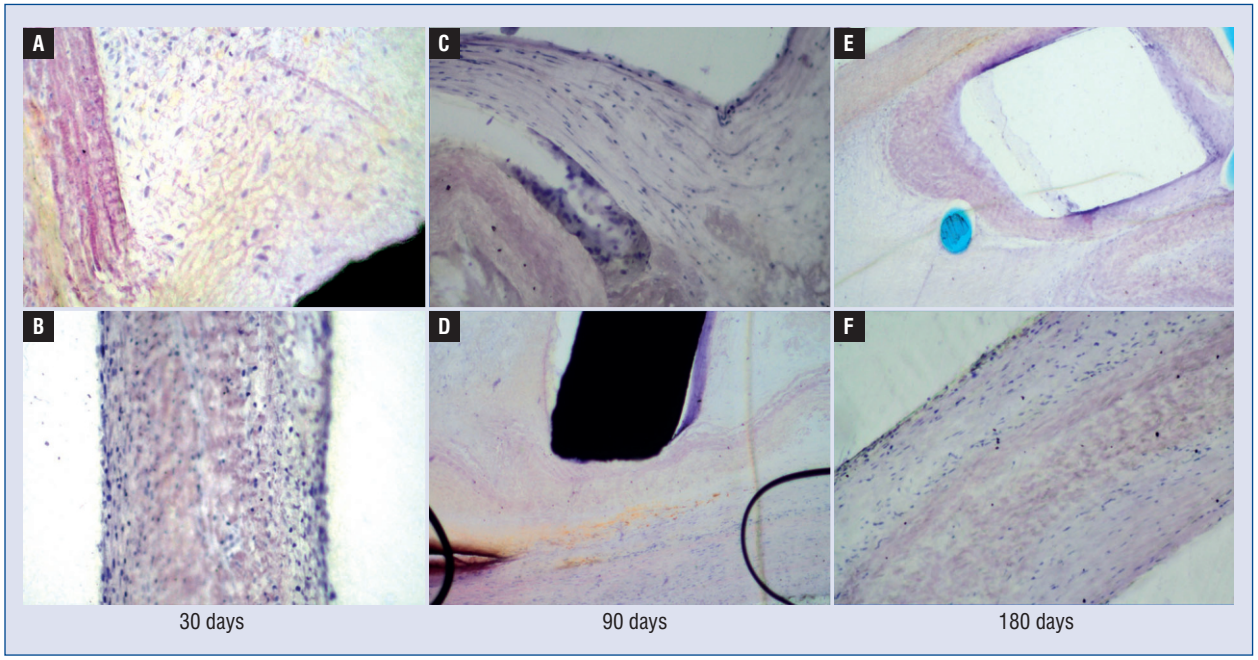

Figure 5. Representative images of microscopical biological response and healing; **A.** Stent (right bottom) hemmed with biological tissues. Visible matrix pattern, cellularity preserved, typical amount of extra-cellular substance; **B.** Biological valve leaflet — preserved cellularity numerous disrupted lymphocytes in the colic, leaflet covered with flattened cells on both sides; **C.** Endothelial cells cover the surface of the valve leaflet, connective tissue stroma, fibrous cell poor; **D.** Stent — no inflammatory reaction at the site of contact; **E.** The outline of the stent. Surrounding tissues are poorly cellular and homogeneous, without inflammatory, fibrotic and non-inflammatory infiltration. Cross section of the surgical suture visible; **F.** The valve leaflet. The correct histological structure of the flap is preserved. The oligocellular stroma. Segmental endothelial coverage.

Discussion

The present study reports the short- and long--term results of a new biological TAVI prosthesis tested in a preclinical setting. Thanks to the utilization of a novel aortic banding model, a repeatable process of valve implantation and anchoring was achieved that allows for a proper assessment of prosthesis functionality, durability and biological response [13]. At terminal follow-up, the tested prosthesis showed optimal functionality in echocardiography, with a decrease in pressure gradients over time and no significant structural valve deterioration. In pathology progressive, temporal stent healing was noted with mature neointima coverage beginning at day 30 and completion of healing being already reported at 90 days. There were no adverse inflammation or leaflet thickening, confirming optimal biocompatibility and functionality of the tested valve.

The cumulative mortality amounted to 33%, which is lower than those reported in a majority of other similar studies [14–16]. Four animals died within the periprocedural period, which was attributed to implantation in a highly placed banding resulting in the prosthesis partially occluding the brachiocephalic trunk or coronary ostia causing cardiac arrest, myocardial infarction or stroke. These incidences were especially prevalent in the first cases performed, where both banding suturing technique and optimal implantation in banding were not yet refined. A situation that changed along with learning curve. During the observation period we reported 2 deaths. First animal underwent a sudden cardiac arrest on day 9, without any abnormalities in necropsy, whereas second animal was found dead on day 63 after a rapid decline of the clinical state — histopathology confirmed endocarditis of the implanted prosthesis.

The performed echocardiography showed good hemodynamic outcomes and no structural valve deterioration of implanted devices at respective time points in all surviving animals. No heavy calcification or large thrombi were observed. The only mean gradients of > 30 mmHg were reported in 2 animals, that were diagnosed with having a significant endocarditis on the prostheses (one of them completed the 30-day follow-up, the other

died prematurely at day 63). The pressure gradients reported were comparable at all time points. The increased pressure gradient in 2 cases, can be related to the initial banding stenosis of around 20–30% of aorta diameter caused by the placing of banding for anchoring purposes. The sutured band has low longitudinal expansion capabilities which results in narrowing being only partially relieved through the TAVI procedure. What is more, as stated in histopathology report, the presence of neointimal pannus covering the stent surface and leaflets to varying degree, could have also influenced the gradient by inducing relative vessel stenosis and slightly impairing leaflet mobility. Lastly, the correlation of animal growth and gradient increase was previously described in other studies [14, 17]. Importantly all valves retained their functionality which was reflected in no severe aortic insufficiency reported across the study.

Histopathology analysis conducted in all 11 animals that completed the observation period revealed proper positioning and valve anchoring in the banding site. Gross inspection showed thin elastic leaflets, without any tears or fenestrations. Only in 1 animal, sacrificed after 30 days follow-up, showed an intramyocardial abscess penetrating to prosthetic elements with subsequent bacterial vegetations was described. Present in such an early phase, this might have been related to accidental procedural contamination. Biological valves displayed no significant calcifications at 180 days, and only minor/punctiform in 4/5 cases at 90 days and 2 in the 30-day group, respectively. Thrombosis was never seen as a pathologically significant process. Flat and scanty thrombi were reported in some prostheses occupying the place between lower basal part of the leaflet, stent strut and aortic wall, similarly to the ones visible in TAVI postmortem observations. All animals sacrificed according to the schedule showed healing and integration features in the cusps characterized by varying coverage of the cusps by endothelialized fibro-cellular neointima that frequently progressed to thicker pannus formation, due to stent apposition to the aortic wall. The inflammatory cell infiltration was reported in 1 animal at 90 days and both sheep at 30 days (one associated with endocarditis) with no foreign body reaction observed in remaining animals, proving an optimal biocompatibility profile of implanted prostheses.

The healing results of Inflow biological prostheses as evaluated in the preclinical setting, with no valve degeneration at 1, 3, and 6-month follow-up is similar to those reported with currently available balloon expandable valves, including the Edwards Sapien device [14, 15] and MyVal [13]. However, in the current study, a higher proportion of valves implanted at baseline reached the terminal follow-up, mostly because of model improvements.

Limitations of the study

The main limitation to be considered is the fact that although aortic banding model was created, the included animals were young and healthy, with no calcific native valve stenosis.

Secondly, as mentioned in the methodology section the prostheses were implanted in the ascending aorta region, pre-prepared with the banding procedure. Surgical intervention did not require the removal of the aortic apparatus, therefore a potential bias attributed to the proper function of a native valve influencing the overall hemodynamic could be perceived.

Conclusions

The study showed a proper hemodynamic performance and acceptable biocompatibility of the novel biological InFlow transcatheter heart valve, comparable to other biological counterparts, as evaluated in the long-term observation in the ovine banding model. The presented prosthesis may be a viable alternative to the currently used biological technologies and add up to the widespread utilization of TAVI procedures.

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Conflict of interest: None declared

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