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ORIGINAL ARTICLE

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ADULT CARDIAC

Apical closure device for full-percutaneous transapical valve implantation: stress-test in an animal model†

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Abstract

OBJECTIVES: Transapical valve implantation is traditionally performed through a left antero-lateral mini-thoracotomy. A self-expandable apical closure device has recently been developed for full-percutaneous transapical valve implantation. We performed haemodynamics stress-tests on an animal model to evaluate the sealing properties.

METHODS: Under general anaesthesia 5 pigs (mean weight: 67 ± 6 Kg) received full heparinization (100 IU/Kg; activated clotting time >250 s and, through inferior mini-sternotomies, 21-Fr introducer sheaths for transapical aortic valve implantation (outer diameter: 25-Fr) were placed over-the-wire in the apexes. Delivery-catheters carrying folded occluders (SAFEX^{TM} final design) were inserted in the introducer sheaths and plugs were then deployed under fluoroscopic guidance. Phase 1: after protamine injection, apical bleeding was monitored for 1 h with standard haemodynamics condition. Phase 2: we induced systemic hypertension with adrenaline infusion to test the sealing properties under stress. Animals were sacrificed after Phase 2 and hearts were removed and inspected.

RESULTS: Five plugs were successfully introduced and deployed in 5 pig hearts. Plugs provided good apical sealing in each animal and a mean of 7 ± 4 ml of blood lost per animal was collected during Phase 1: haemodynamics remained stable and no plug dislodgement was detected (mean blood pressure: 52 ± 9 mmHg). During Phase 2, mean systolic and diastolic peak levels reached 268 ± 24 mmHg and 175 ± 17 mmHg, respectively, without plug dislodgment or bleeding. Post-mortem inspection showed good plug deployment and fixation without myocardial damage.

CONCLUSIONS: The new apical occluder seals large-sized apical access sites in animal models also during induced systemic hypertension. This pilot study is a further step towards full-percutaneous transapical valve procedures in the clinical setting.

Keywords: Transcatheter valve implantation • Transapical valve implantation • Apical closure device • Percutaneous heart valve procedures

INTRODUCTION

Complex structural heart procedures and transcatheter aortic and mitral valve implantation (TAVI and TMVI) can be performed transapically through a left antero-lateral mini-thoracotomy at the fifth intercostal space and the apex is traditionally prepared with a double reinforced purse-string suture or multiple reinforced U-shaped stitches. For the time being, standard introducer sheaths or delivery-catheters employed in TAVI/TMVI have an outer diameter ranging from 22-Fr to 35-Fr. However, despite the arrival of new low-profile introducer sheaths and new delivery catheters, the apical access remains a challenge in old patients due to the risk of infection, myocardial damage, ventricular tear and major/life-threatening bleeding [1]. Moreover, the standard apical access represents a limit for the development of video-assisted thoracoscopic TAVI/TMVI or full-percutaneous transapical valve procedures.

Recently, some apical closure devices for transapical TAVI/TMVI have been developed and tested with encouraging results [2–4]. Unfortunately, the Apica^{TM} ASC device (Apica Cardiovascular, Galway, Ireland) was recently discontinued and the only available device approved for clinical use in Europe is the Permaseal^{TM} (Micro International Device, Newtown, PA, USA). However, only few

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prototypes fulfil selective requirements for lesser invasive or full-percutaneous transapical valve implantation and the Permaseal™ still requires a mini-thoracotomy to expose the apex. Therefore, a new self-expandable apical occluder has been recently developed for full-percutaneous transapical valve implantation with large-size introducer sheaths.

After previous pilot studies with modified ventricular septal defect occluders [5–8] and after our preliminary report on efficacy and safety of the new apical occluder (the prototype) in an animal setting [9], we have tested the sealing properties of the device's final design under stress.

MATERIALS AND METHODS

This pilot study is an acute animal model involving pigs and performed under general anaesthesia in the animal lab (Cardiovascular Research Unit, University Hospital of Lausanne, Lausanne, Switzerland). The efficacy of the self-expandable plug in sealing large-size apical access sites was tested at first in standard haemodynamics condition (Phase 1) and then during a stress-test induced by high-doses of adrenaline (Phase 2).

The SAFEX™ apical occluder

The SAFEX™ apical occluder from Comed (Comed, Bolsward, Netherlands) has reached its final design (Fig. 1). It is made of woven Nitinol wires designed in two self-expandable round retention disks with a connecting extendable waist. The surfaces of the discs are slightly curved to better adapt with the ventricular anatomy. Inside the two disks there are two membranes of expanded polytetrafluoroethylene that provide at first a mechanical occlusion of the apical access sites and subsequently the blood clotting for acute and long-term haemostasis. With regards to the risk of potential thromboembolic events, animal tests in a chronic setting will be performed in a near future.

Figure 1: The self-expandable SAFEX™ apical occluder with the extendable and flexible waist (Comed, Bolsward, The Netherlands).

The device is expected to occlude apical access sites ranging from 20-Fr to 35-Fr diameter with 4 different sizes that will become available in the future. The specific design allows a simple and user-friendly two-step manoeuvre for the deployment through large-size sheaths under fluoroscopic control (Fig. 2). Specifications for the device employed during this test are as follows: inner disk of 18 mm diameter, outer disk of 16 mm diameter, connecting extendable waist of 10 mm diameter and 8 mm long.

The delivery system

The occluder is screwed to a wire and inserted into a 10-Fr size (outer diameter of 13-Fr), 40-cm long delivery system from Comed. During standard transapical valve implantation, this delivery-catheter allows the placement of the SAFEX™ into the left ventricle using the large-sized introducer sheaths previously employed to deliver and implant the aortic or the mitral stent-valve.

Animal preparation

Five pigs (race: domesticus pig; mean weight: 67 ± 6 Kg) were used for this pilot study. Animals received care in compliance

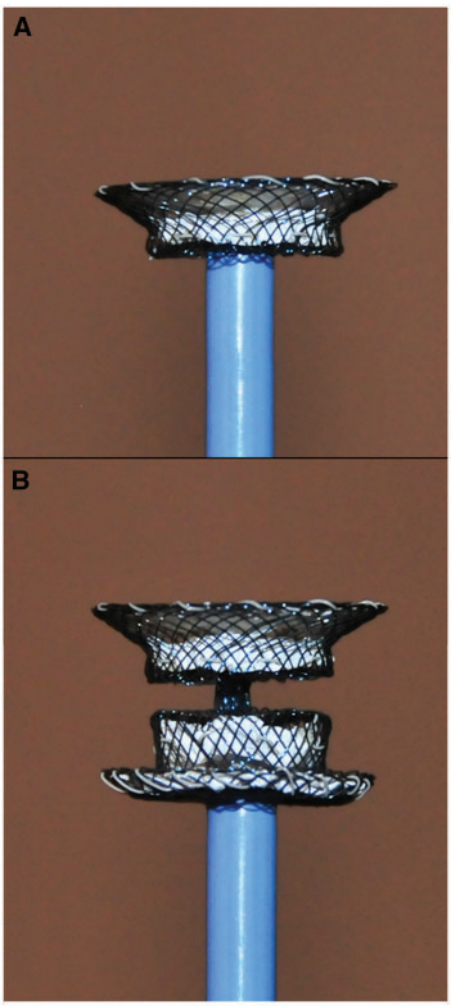


Figure 2: The two-step manoeuvre for the deployment of the new SAFEX™ apical occluder. (**A**) Step 1: the inner disk opens when the sheath is partially retrieved. (**B**) Step 2: the outer disk opens when the sheath is fully retrieved.

with the 'Principles of Laboratory Animals' formulated by the National Society of Medical Research and the 'Guide for the Care and Use of Laboratory Animals' prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 85–23, revised 1985). The protocol was approved by the local Committee on Animal Research (Protocol number: 1708.4).

After undergoing general anaesthesia with tracheal intubation and mechanical ventilation (Ketamine 10 mg/kg, Atropine 1 mg/kg and Xylazine 0.1 mg/kg for premedication; Propofol 4 mg/kg and Isoflurane for anaesthesia induction; Isoflurane 1.5–2.5% for maintenance of anaesthesia), the right carotid artery and the internal jugular vein were prepared and used to monitor the blood pressure (BP), the central venous pressure, as well as for blood sampling, blood gas analysis and for fluid or drug infusions.

Haemodynamics monitoring

Electrocardiography, BP (systolic, diastolic and mean arterial pressure), the central venous pressure, heart rate and oxygen saturation were continuously monitored and then recorded every 10 min during Phase 1, and every 5 min during Phase 2. Activated clotting time measurements were performed at baseline and 2 min after heparin and protamine administration [10]. Activated clotting time was maintained above 250 s during wire and catheter insertion, during delivery of the occluder and during the removal of the sheath and occluder deployment. Blood gas analysis was performed at baseline and during Phases 1 and 2.

The animal study

Preparation. After an inferior mini-sternotomy (to expose the left ventricular apex that lies, in pigs, underneath the distal part of the sternum) and full heparinization (Liquemine, Drossapharm AG, Basel, Switzerland: 100 IU/kg), the pericardium was opened and the cardiac apex was lifted and exposed using pericardial sutures. To prevent bleeding from sternum and mediastinum, a lot of care was used to coagulate all cut vessels and tissues with the electro-cauteriser. Pleura and peritoneal cavities were not opened in order to prevent blood accumulation. Under fluoroscopic control, the apex was punctured and a standard guidewire was placed in the left ventricle followed by the insertion of a 21-Fr Certitude^{TM} introducer sheath for Sapien^{TM} 3 aortic valves (Edwards Lifescience, Irvine, CA, USA) (outer diameter: 25-Fr). The mandrel and the guidewire were removed and the delivery system carrying the folded SAFEX^{TM} occluder was inserted into the sheath and placed into the left ventricle (Fig. 3A and B).

The two-step manoeuvre. Step 1: under fluoroscopic control, the inner disk was deployed into the left ventricle and pulled back (together with the delivery catheter) towards the Certitude^{TM} and the internal apical wall in order to provide apical sealing from inside (Fig. 3C and D). The tactile feedback and the fluoroscopy confirmed the success of this manoeuvre. Step 2: The introducer sheath and the delivery catheter were pulled back together while the wire connected to the occluder was left in place and the outer disk opened outside the apex (Fig. 3E). Then, the wire was unscrewed and disconnected (Fig. 3F). More technical details were presented in a previous report [9].

Phase 1 (1 h). After having neutralized the heparin with protamine chloridrate (Protamine Ipex 1000, MEDA Pharmaceuticals SPA, Milan, Italy), the blood in the pericardium was collected for a period of time of 1 h with standard haemodynamics condition (no low pressure induces to minimize the blood loss). During this hour, haemodynamics parameters were surveyed, maintained

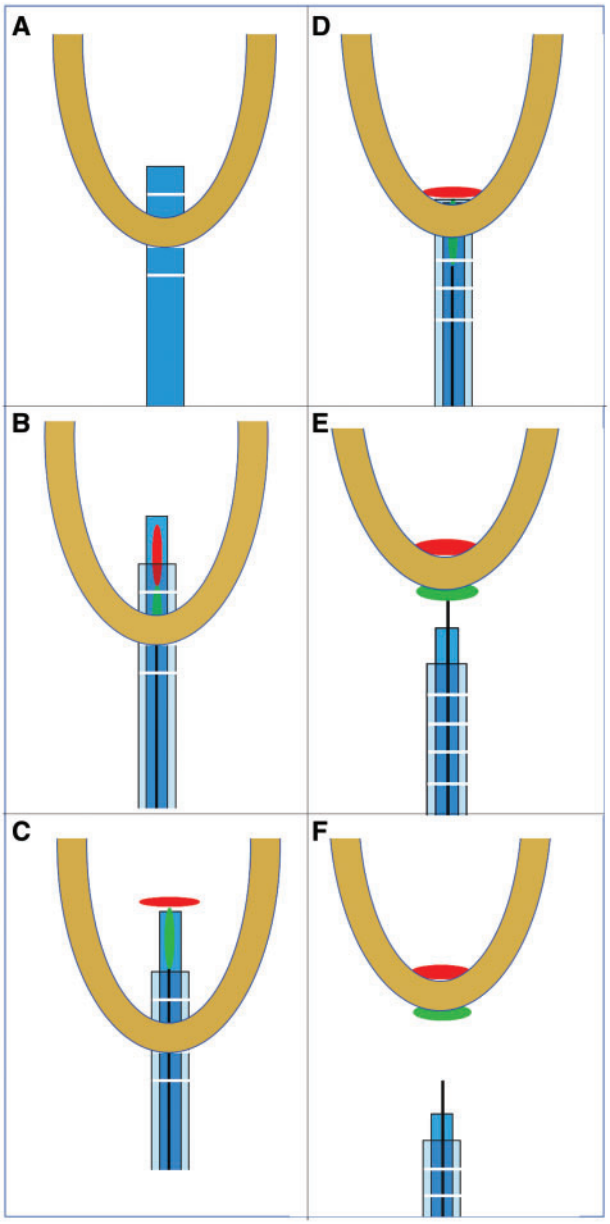


Figure 3: Schematic view of the two-step manoeuvre for the deployment of the apical closure device. (**A**) The Certitude^{TM} introducer sheath is placed in the apex. (**B**) The delivery system with the folded occluder is inserted in the left ventricle through the introducer sheath. (**C**) Step 1: the inner disk of the SAFEX^{TM} apical closure device (in red) is deployed into the left ventricle. (**D**) The inner disk is pulled back towards the introducer sheath and then all systems are pulled back until the inner disk is in contact with the apex. (**E**) Step 2: the introducer sheath and the delivery system are pulled back together while the wire connected to the occluder remains in place. The outer disk (in green) opens and occludes the access site. (**F**) The wire is unscrewed and the device is released.

stable and recorded every 10 min. After 1 h, the accumulated blood loss and clots were drawn and measured (mL).

Phase 2 (30 min). After the 1 h observational period with standard haemodynamics condition, a continuous intravenous adrenalin infusion (Adrenalin Sintetica, Sintetica SA, Mendrisio, Switzerland) was set up. Every 5 min and for 6 occasions (30 min in total) the adrenalin dose was doubled (10 mcg/min; 20 mcg/min; 40 mcg/min; 80 mcg/min; 160 mcg/min; 320 mcg/min) while BP, the central venous pressure and heart rate were monitored and recorded. The intrapericardial accumulated blood loss was drawn and measured at the end of Phase 2. After Phase 2, animals were sacrificed with intravenous injections of 200 mg/Kg of sodium pentobarbital (Nembutal by Abbott Laboratories, Chigago, IL, USA).

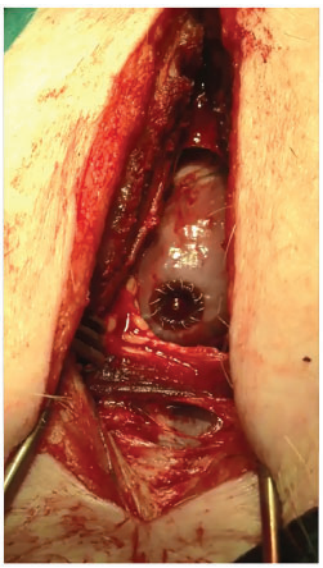
Explanted hearts. After Phase 2, animals were sacrificed and hearts were explanted to inspect the occluders (full deployment, positioning evaluation) and to analyse the interaction with the surrounding myocardium.

Statistical analysis

Variables are reported as mean ± one standard deviation.

RESULTS

Procedural success rate was 100% at first attempt in all animals. Immediate good apical sealing was always obtained after having removed the sheath, deployed the plug and injected the protamine. No major or life-threatening bleedings were detected after protamine infusion (Video 1). Haemodynamics parameters were stable during Phase 1 of this protocol, with mean heart rate of 87 ± 14 beats per minute and mean arterial mean BP of 52 ± 9 mmHg. During the 1-h observation period with normal haemodynamics condition (Phase 1), blood loss from the surgical site was drawn from the pericardium and measured with an average amount of 7 ± 4 ml of blood lost per animal (Animal 1: 10 ml, Animal 2: 7 ml, Animal 3: 10 ml, Animal 4: traces/unmeasurable, Animal 5: 7 ml). The blood loss came, mainly, from the mediastinum and the sternum and this was confirmed by the continuous inspection of the apex that did not show blood loss from the occluder or from the surrounding myocardium. Mean haemoglobin levels at baseline, after the occluder's deployment and at the end of the 1-h observation period were 8.4 ± 0.8 g/dl, 8.2 ± 0.6 g/dl and 8.7 ± 0.8 g/dl, respectively.



Video 1: Surgical view from the inferior mini-sternotomy showing the SAFEX^{TM} apical occluder in place.

During Phase 2, mean systolic and diastolic BP levels reached peaks of 268 ± 24 mmHg and 175 ± 17 mmHg respectively, without plug dislodgment or bleeding (unmeasurable traces). The systolic, diastolic and mean BP of each pig involved in the pilot study was recorded during Phase 1 and Phase 2 and shown in Table 1 and Fig. 4. Post-mortem heart inspection confirmed the good deployment and positioning of the occluders without macroscopic myocardial injuries (Fig. 5).

DISCUSSION

Full-percutaneous or video-assisted transapical valve procedures with big-sized introducer sheaths cannot be performed with the existing technology, and this is a limit for the development of future transapical standards. The use of new introducer sheaths and low-profile delivery catheters is a good strategy to minimise the impact of this technique but only the development of new apical occluders that can be delivered and deployed without opening the chest will allow the development of full-percutaneous TAVI/TMVI.

The SAFEX^{TM} apical occluder fulfils all criteria for use during full-percutaneous transapical valve implantations and, during this pilot study, it has been tested in stressful haemodynamics conditions with good results in terms of safety (no dislodgement, good positioning, no myocardial damage) and efficacy to seal big-sheath apical access sites. This finding confirms our previous report where the plug provided good apical sealing without myocardial damage and bleeding after the removal of the introducer sheath [9]. Moreover, during the tests the device was easy to deploy with a user-friendly two-step manoeuvre.

Interestingly, during the test we noticed that a certain amount of blood leaked from inside the big-sized introducer sheath when the sheath was retrieved from the apex and the outer disk of the occluder deployed (at the end of step 2). Since that moment and after the protamine injection, there were only traces of blood coming through the SAFEX^{TM} occluder, and this leakage stopped after few seconds. Then, there was no blood loss from the occluder also when the intraventricular end-systolic pressure increased with adrenaline infusion. Therefore, we can figure out that during future full-percutaneous transapical valve implantation in a clinical setting a little pericardial drain will be placed, percutaneously, during the procedure in order to draw the limited amount of blood leaking during the big-sized introducer sheath removal and prevent cardiac tamponade.

To what may concern the risk of thrombogenicity in the near future we will perform chronic tests in an animal model. In fact, we can speculate that the inner disk will be covered by neo-endothelium and a 3-month oral anticoagulation therapy or double antiplatelet treatment will prevent thromboembolic events as it happens after the placement of ventricular septal defect occluders. But this has yet to be proven.

Table 1: Systolic, diastolic and mean blood pressures of each pig measured during Phase 1 and Phase 2 of the pilot study

	Animal	1			2			3			4			5		
	Blood pressure	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
	Baseline	86	57	67	60	30	38	81	51	61	88	47	59	73	31	46
	Sheath inserted	87	56	67	87	56	67	70	39	48	76	42	48	75	32	49
	Occluder deployed	68	41	50	72	41	51	70	36	47	71	35	44	73	34	49
Phase 1	10 min	66	39	48	70	37	46	65	33	42	72	35	44	78	38	54
	20 min	80	50	60	69	37	46	74	41	52	74	37	48	70	34	46
	30 min	80	49	60	78	45	55	76	43	55	65	32	42	75	32	47
	40 min	78	54	60	78	45	55	77	46	50	70	37	46	78	36	50
	50 min	77	48	56	79	45	56	73	39	51	77	40	52	72	33	45
	1 h	74	45	55	80	46	57	63	29	39	78	42	54	71	31	43
Phase 2	Adrenaline 10 mcg/min	113	78	90	89	56	68	78	41	55	96	75	73	109	45	64
	Adrenaline 20 mcg/min	170	130	145	129	96	107	85	50	75	132	79	100	124	92	110
	Adrenaline 40 mcg/min	201	149	163	152	115	133	121	93	108	170	104	127	165	108	129
	Adrenaline 80 mcg/min	211	153	172	175	120	130	140	114	126	200	122	150	191	126	151
	Adrenaline 160 mcg/min	217	157	176	226	155	183	197	137	165	233	143	180	220	141	168
	Adrenaline 320 mcg/min	268	162	199	241	173	203	244	189	218	244	175	208	263	160	200

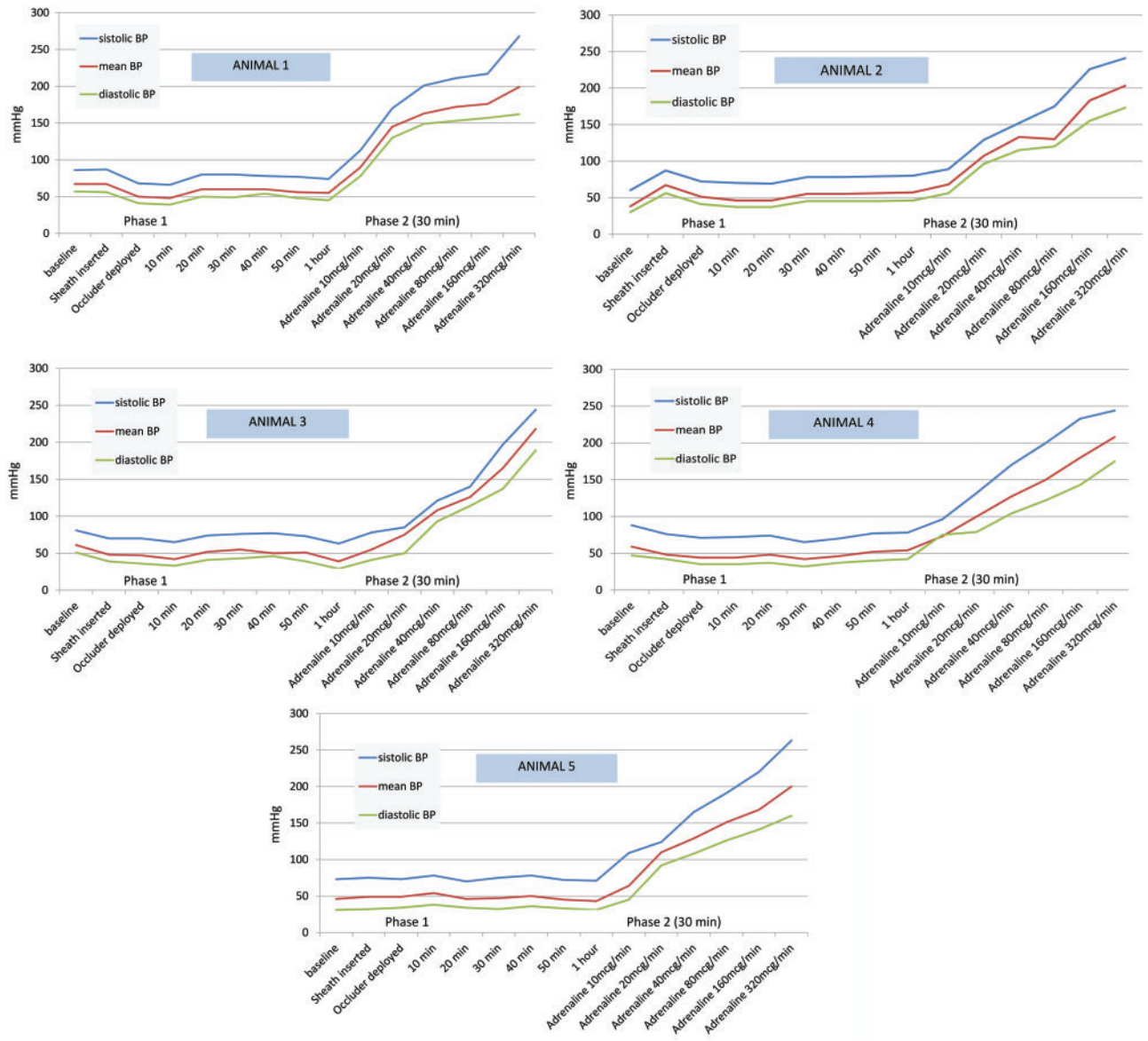


Figure 4: The graphics show the measured systolic, diastolic and mean blood pressures of each pig measured during Phase 1 and Phase 2.

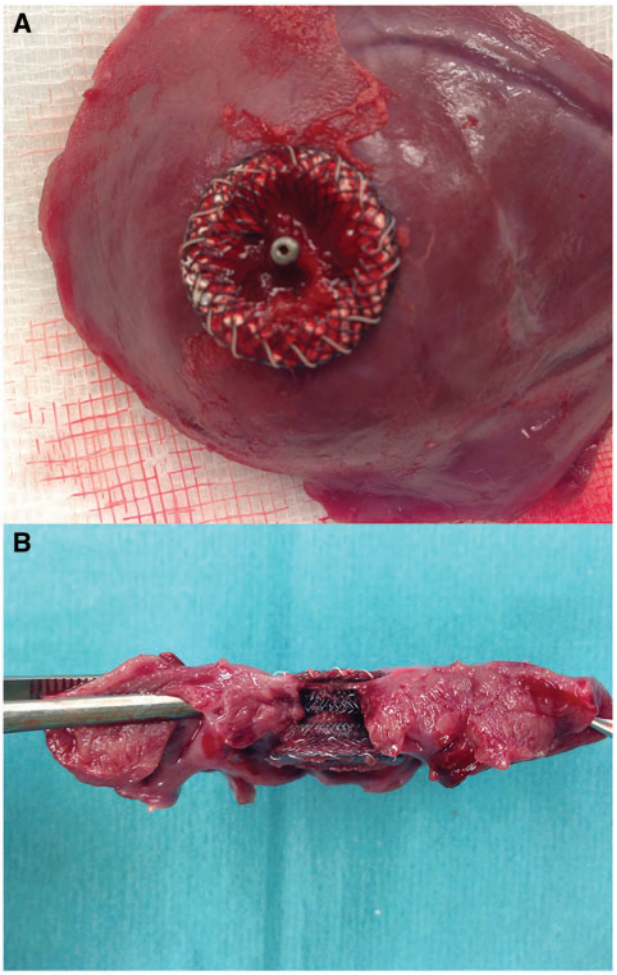


Figure 5: Visual examination of an explanted pig heart. (**A**) External view of the apex showing the occluder in place. (**B**) Lateral view showing the occluder in place, with the inner (bottom) and the outer (top) disks fully deployed. Macroscopic myocardial injuries were not detected.

Comparing the self-expandable SAFEX^{TM} occluder to the only available device approved for clinical use in Europe, the Permaseal^{TM}, we can see major differences in size (the Permaseal^{TM} being bigger than the Safex^{TM}, limiting its use in full-percutaneous procedures), design (The Permaseal^{TM} is a gun-shaped device delivering 8 connected little anchors around the apical access site), engineering (the Permaseal^{TM} releases the 8 anchors using a pre-charged automatic system while the Safex^{TM} employs a manual two-step manoeuvre), and in the way the system anchors to the myocardium and occludes the access site (the Permaseal^{TM} uses 8 little anchors inserted in the myocardium, around the access site, that are kept close by a suture that has to be pulled and knotted by the surgeon while the Safex^{TM} occludes the access site from inside as a high-tech bottle cap) [4]. Moreover, the Permaseal^{TM} still requires a mini-thoracotomy and is not supporting thoracoscopic or full-percutaneous transapical valve implantation.

However, it can be used with sheathless transcatheter valve systems. In fact, the Safex^{TM} privileges transcatheter valves placed through large-sized introducer sheaths, such as the Sapien^{TM} valve with the 21-Fr Certitude^{TM}, but, in the perspective of future full-percutaneous TAVI/TMVI, sheathless stent-valve systems would also be employed using larger-size introducer sheaths that convoy the delivery-catheters.

Limits of the present study are the acute animal setting, the limited number of animals and the apical approach performed through an inferior mini-sternotomy. Chronic animal tests in a minimally invasive setting are already scheduled and will focus on the SAFEX^{TM} thrombogenicity, ventricular function and potential rhythm disturbances. Full-percutaneous tests in animals to establish the technical platform for future clinical use in humans are planned.

In conclusion, the SAFEX^{TM} apical occlude from Comed is efficient under standard and stressful haemodynamics conditions and this pilot study represents a further step towards less invasive and full-percutaneous transapical valve implantations.

Funding

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Conflict of interest: Enrico Ferrari is co-inventor of the SAFEX^{TM} apical occluder and he is a consultant for Comed.

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