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Transvenous implantation of the Occlutech Atrial Flow Regulator: Preliminary results from swine models

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Abstract

Aims: To evaluate in domestic pigs the histopathological processes after implanting the Occlutech Atrial Flow Regulator (AFR).

Methods and Results: Eleven pigs were chosen and had successful implantation of the AFR. Five pigs were sacrificed at 28 days, and 5 pigs at 90 days. One pig was sacrificed at day 3 after device embolization. Each pig had echocardiography performed at 3 weeks to check patency. Post mortem evaluation included Gross evaluation, radiographic evaluation, histology, and electron microscopy. Nine of the 10 devices implanted remained patent at time of autopsy with no thrombus and minimal inflammation. One device placed in the PFO closed by day 28 and the other embolized on day 3.

Conclusion: The Occlutech AFR has shown to be safe and easy to implant with good results [Krizanic et al. *J Invasive Cardiol*. 2010;22(4):182.]. This study has further shown that histologically the device does not cause any end organ damage, causes minimal inflammation, with almost no thrombus formation and can remain patent and secure in the atrial septum.

KEYWORDS

atrial flow regulator, atrial septostomy, left atrial hypertension, pulmonary hypertension

1 | INTRODUCTION

Pulmonary arterial hypertension and left ventricular diastolic failure are diseases in which high diastolic ventricular and hence atrial pressures can lead to poor cardiac output and atrial distension resulting in decreased functional capacity, arrhythmias, and premature death. The methods and logic of offloading the hypertensive atrium into the contralateral atrium in these diseases have been the subject of much debate.[1-3]

In patients with pulmonary hypertension and left ventricular diastolic dysfunction as well as certain congenital heart defects, an atrial communication may be beneficial to maintain cardiac output. An atrial communication created by an atrial septostomy (AS) has been shown to be an effective intervention in selected patients with PAH.[1,2] AS performed in patients on PAH-specific pharmacotherapy was shown to improve both hemodynamics and symptoms while increasing long-term survival.

There are two major practical problems associated with AS in patients with PAH. Creating a reliable, sustainable communication, and creating an atrial defect that is just the right size; neither too small nor too large. Atrial communications that are too large are associated with early mortality and profound cyanosis whereas too small a communication is more likely to close spontaneously and not alleviate the symptoms or improve prognosis.[1] Heterogeneity of the atrial septal geometry and tissue makes it difficult to achieve consistent and predictable results with each AS and balloon dilation. Although atrial septal stenting may promise a more physiologically predicable communication, it is a more complex procedure bringing a different range of technical and follow-up issues.[3]

The Atrial Flow Regulator (AFR) (Occlutech, Istanbul, Turkey) (Figure 1) is a double disc device made of self-expanding Nitinol wire mesh. Its design is an amalgamation of a self-expanding stent, a vascular plug and a fenestrated ASD occluder. The device is structured around a central lumen, intended to maintain a patent

FIGURE 1 The occlutech atrial flow regulator

communication. Once deployed via the transfemoral route, the central portion stents the atrial septum leaving a preselected fixed diameter atrial communication. Despite several case reports and small case series, suggesting significant improvements in symptoms, six-minute walk test, cardiac index, and systemic oxygen transport, the device is yet to undergo a rigorous scientific trial, and the long-term patency rates and mechanisms of occlusion have not been defined.[2]

The main purpose of this study is to evaluate the technical implantation efficacy, safety, and short-term patency of the AFR by implanting them in healthy porcine hearts for 28 and 90 days.

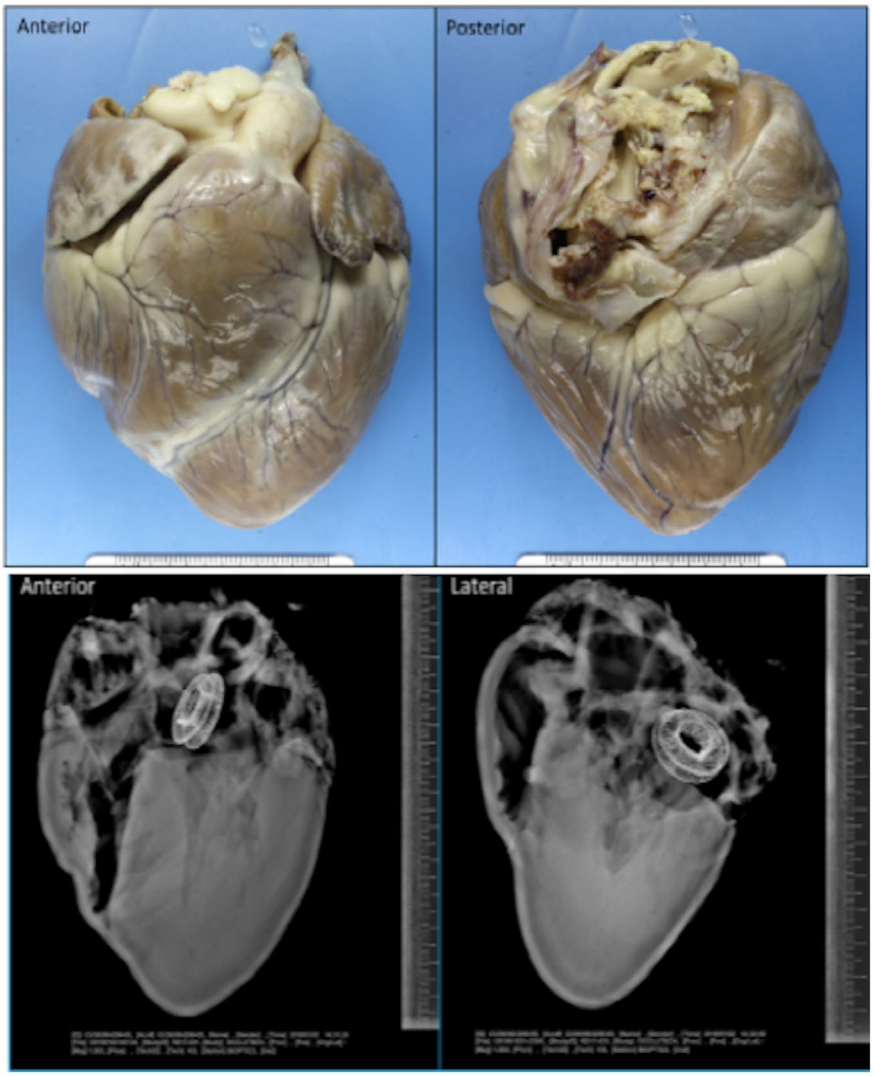


FIGURE 2 Gross specimen and radiograph of the whole heart in Pig A

TABLE 1 Histological tissue response scores by section for pigs sacrificed Day 28

Pig	Side	Section	Neointimal tissue growth score	Granulation tissue score	Fibrin/Thrombus score	Inflammation severity/Extension score
Pig A	Right	Anterior	1	1	0	1
		Mid	1	1	1	1
		Posterior	2	1	0	1
	Left	Anterior	2	1	0	1
		Mid	0	0	1	2
		Posterior	2	1	0	1
Pig B	Right	Anterior	4	3	0	2
		Mid	1	1	1	2
		Posterior	4	1	0	2
	Left	Anterior	2	3	0	2
		Mid	1	1	0	2
		Posterior	2	2	0	1
Pig D	Right	Anterior	4	1	0	1
		Mid	4	1	0	1
		Posterior	4	0	0	1
	Left	Anterior	4	1	0	1
		Mid	4	1	0	1
		Posterior	4	1	0	1
Pig E	Right	Anterior	1	1	0	2
		Mid	1	1	0	2
		Posterior	2	1	0	1
	Left	Anterior	1	1	0	2
		Mid	0	1	0	2
		Posterior	1	1	1	1

Histologic assessment of the device was conducted after euthanasia, to quantify and characterize reactive tissue growth, granulation tissue, fibrin/thrombus formation, endothelialization, and severity of inflammation.

2 | METHODS

2.1 | Device description

The AFR is a self-expanding nitinol wire mesh device consisting of a short central stent between two circular discs. The device is intended for transfemoral deployment, following trans-septal perforation and static balloon dilation to aid delivery and minimize compression of the central stent portion (Figure 1). A spherical ball and socket type connector is located off-center on the device's right atrial disc to connect the delivery system for deployment. After implantation, the AFR is designed to conform flush to either side of the atrial septum leaving an interatrial communication with a preselected fixed diameter. The device self-centers following deployment and is retrievable prior to release. Following release retrieval of the device is feasible in a similar manner to other Occlutech devices.[4] The fenestration diameters range from 4 to10 mm at 2 mm increments. The device is available with three central stent lengths: 2, 5, and 10 mm to suit the atrial septal thickness.[3]

2.2 | Procedure

The AFR was implanted in 11 adolescent domestic pigs (sus scrofa domestica), who were pre-treated with Aspirin on the day of the procedure and maintained on aspirin until euthanasia. The pigs were placed under general anesthesia for the procedure. After induction of anesthesia, the right and left femoral veins were accessed via bilateral inguinal incisions with 8Fr sheaths. A Siemens Acuson AcuNav Intracardiac echocardiography (ICE) catheter (Siemens, Mountain View, CA, USA) was inserted and used to guide the procedure. An 8Fr SL- 1 Schwartz Braided Trans septal sheath (St Jude Medical, Minneapolis, MN, USA) was placed in the right femoral vein. Through this a BRK 1 extra sharp transseptal needle (St Jude Medical, Minneapolis, MN, USA) was fed and an atrial septal puncture was made. A 0.035″ Amplatz Super Stiff wire (Boston Scientific, Natick, MA, USA) was placed through the sheath and into either a

TABLE 2 Histological tissue response scores by section for pigs sacrificed Day 90

Pig	Side	Section	Neointimal tissue growth score	Granulation tissue score	Fibrin/Thrombus score	Inflammation severity/ Extension score
Pig F	Right	Anterior	4	1	0	1
		Mid	4	1	0	1
		Posterior	4	1	0	1
	Left	Anterior	2	1	0	1
		Mid	3	1	0	1
		Posterior	2	1	0	1
Pig G	Right	Anterior	3	1	0	1
		Mid	4	1	0	1
		Posterior	4	1	0	1
	Left	Anterior	4	1	0	1
		Mid	4	1	0	1
		Posterior	3	1	0	1
Pig H	Right	Anterior	4	1	0	1
		Mid	2	1	0	1
		Posterior	4	1	0	1
	Left	Anterior	2	1	0	1
		Mid	2	1	0	1
		Posterior	1	1	0	1
Pig J	Right	Anterior	4	2	0	1
		Mid	4	1	0	1
		Posterior	4	2	0	1
	Left	Anterior	4	1	0	1
		Mid	4	1	0	2
		Posterior	4	2	0	1

pulmonary vein, or if this was not possible the wire was curled in the left atrium. A Conquest angioplasty balloon (Bard Peripheral Vascular, Inc., Tempe, AZ, USA) with diameter equal to or 2 mm larger than the planned AFR was inserted and used to predilate the septum. The SL-1 was then removed and exchanged for a proprietary 12Fr delivery sheath. The same-sized AFR was implanted into each pig (8 mm fenestration diameter and 5 mm waist length) (Figure 2). The AFR was loaded onto the delivery system cable as shown was deployed in the usual manner for Occlutech devices, which has been previously reported.[5] The ICE catheter was then used to evaluate flow through the AFR and to assess position and relative anatomy. Three weeks following device deployment all pigs had follow up trans-thoracic echocardiography (TTE) to assess flow.

Five pigs were euthanized at 28 ± 1 days, and five pigs at 90 ± 1 days. One pig had a large PFO which inhibited our ability to perform a transeptal puncture; therefore the device was implanted in the PFO. This device embolized the animal and was euthanized day 3 post implantation.

Radiographs of the explanted hearts were taken to assess position and potential issues. Gross examination was then performed. Plastic histology was undertaken with a graded series of ethanol and then embedded in Spurrs' resin. The specimens were then segmented into 82-99 micron blocks. Ground sections were then polished and stained with Hematoxylin and Eosin (H&E) and light microscopy was performed. The histology was then scored for signs of inflammation, neointimal growth and more (see Tables 1-3). Selected specimens were then further trimmed and processed before Scanning Electron Microscopy was performed using scanning electron microscopes. The specimens were further processed before paraffin histology was undertaken.

3 | RESULTS

All 11 animals had successful device deployment. One pig was noted to have no flow through the fenestration immediately post deployment. A repeat transeptal needle puncture was performed through the lumen of the device, followed by balloon dilation of the lumen. This was successful at re-opening the lumen of the device. The acute occlusion was felt to be secondary to non-ideal placement of the device between the primum and secundum septums, perhaps within a PFO tunnel leading to occlusion of the device lumen by the primum septum. Another pig

TABLE 3 Description of semi-quantitative histology scores and inflammation-extension severity score: Individual scores were performed for both right and left sides of AFR positioned in the atrial septum

Attribute	Score	Description of assigned scores		
Neointimal tissue growth	0	Absence of neointimal coverage		
	1	<25%		
	2	25% to 50%		
	3	50% to 70%		
	4	>75%		
Granulation tissue	0	Absence of granulation tissue		
	1	<25%		
	2	25% to 50%		
	3	50% to 70%		
	4	>75%		
Fibrin/Thrombus score	0	Absence of surface fibrin and/or thrombus		
	1	Minimal, involving <10%		
	2	Mild, involving 10% to 25%		
	3	Moderate, involving 25% to 50%		
	4	Severe, involving >50%		
Extend of inflammation	Inflammation			
	<25%	>25% to 50%	>50% to 75%	>75%
0	0	0	0	0
1	1	1	1	1
2	1	1	2	2
3	2	2	3	4
4	2	3	4	4

Notes: Inflammation severity scale is defined as: 0 = no inflammation; 1 = minimal/rare 1 to 5 cells per high power field; 2 = mild (5 to 10 cells per high power fields); 3 = moderate, heavy infiltrates; and 4 = severe, packed cells.

was noted to have a large PFO. Per study protocol, all pigs once anesthetized were included in the study, hence the decision was to place the device within the large PFO. The device embolized within 24 hours of placement and the pig was sacrificed day 3 post implantation.

3.1 | Echocardiography at 3 weeks

Follow-up echo of the 10 live pigs at 3 weeks demonstrated a patent lumen in all devices. There was no evidence of obstruction to flow or reduction in lumen caliber. No pigs had evidence of any intracardiac thrombi. There was no obstruction to pulmonary or systemic venous return and all valves were functioning normally. Ventricular function was normal in both ventricles.

3.2 | Radiography and gross specimen evaluation

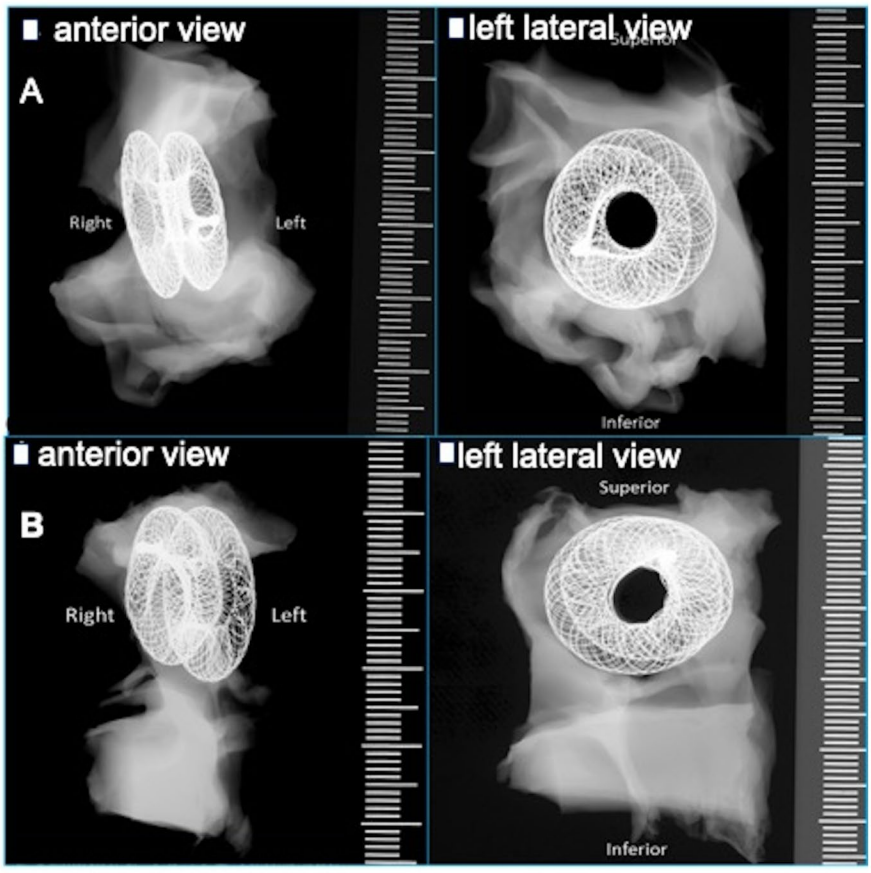
3.2.1 | Pigs sacrificed at 28 days

At 28 days radiographs demonstrated that all devices remained intact and there were no structural problems, specifically no fractures identified in any devices (Figures 2 and 3). Gross evaluation showed that all devices were placed centrally in the atrial septum, clear of related structures such as the mitral valve, tricuspid valve, and pulmonary veins. Overall, the AFR devices at 28 days post implant showed partial incorporation within the atrial septum at the device edges where it was flush with the atrial septum (Figure 4).

Neointimal device overgrowth was mild to moderate, partially covering both surfaces of the AFR in three out of five animals (PIG A, PIG B, and PIG E), greater in areas of device contact with the atrial endocardial surface. In PIG C, there was only minimal evidence of neointimal tissue on the discs. The lumen of the device showed partial coverage of the nitinol struts along the internal surface of the connecting waist with neointimal tissue. The lumen remained widely patent in 4 out of 5 animals (PIG A, PIG B, PIG C, and PIG E). PIG D showed complete closure of the AFR lumen with extensive endocardial (fibro-collagenous) tissue covering the lumen. In only this animal, the right and left atrial surfaces of the device were completely covered by neointimal tissue. The neointimal coverage consisted of granulation tissue, with focal areas of smooth muscle cells some fibrin and proteoglycan matrix (healing score of 1).

3.2.2 | Pigs sacrificed at 90 days

Radiography and gross examination of the explanted specimens again showed that the implanted devices were intact, remote from



Faxitron radiograph images. The AFR device is intact and without evidence of fractures at 28 days in picture A and 90 Days in picture B

FIGURE 3 Radiograph of the AFR at 28 days and 90 days

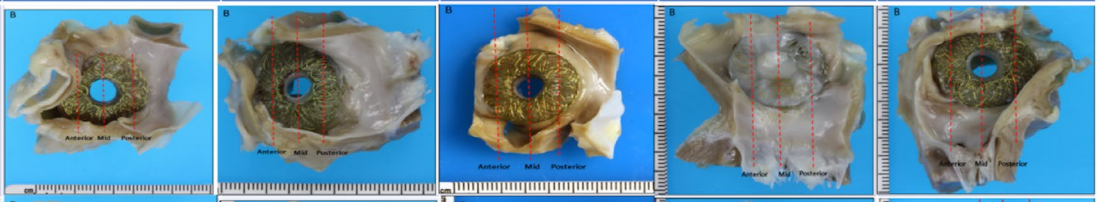
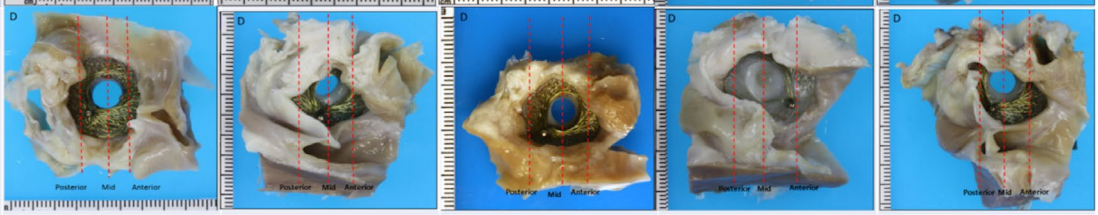
	Pig A	Pig B	Pig C	Pig D	Pig E
Left Atrial View					
Right Atrial View					
Gross Evaluation	The device fenestration is widely patent and is lined by tan-white tissue. Device sits 10mm from mitral annulus, 12mm from left pulmonary veins and 12mm from right pulmonary veins	The device fenestration is lined by tan white tissue with slight narrowing of the shunt, measuring 4-5mm in diameter. Device sits 10mm from mitral annulus, 7mm from left pulmonary veins and 12mm from right pulmonary veins	The device fenestration is widely patent and lined by tan-white tissue, Device sits 7mm from mitral annulus, 8mm from left pulmonary veins and 15mm from right pulmonary veins	The device fenestration is entirely covered by neoendocardial tissue, occluding the shunt. Device sits 11mm from mitral annulus, 9mm from left pulmonary veins and 9mm from right pulmonary veins	The device fenestration is patent and lined by tan tissue. Device sits 10mm from mitral annulus, 12mm from left pulmonary veins and 12mm from right pulmonary veins

FIGURE 4 Gross evaluation of the AFR in pigs sacrificed at day 28

related structures and well-seated in the interatrial septum, partially covered by neoendocardial tissue (Figures 2 and 3). Neointimal overgrowth was mild to moderate, partially covering both surfaces of the AFR in the five animals assessed, with neointimal tissue

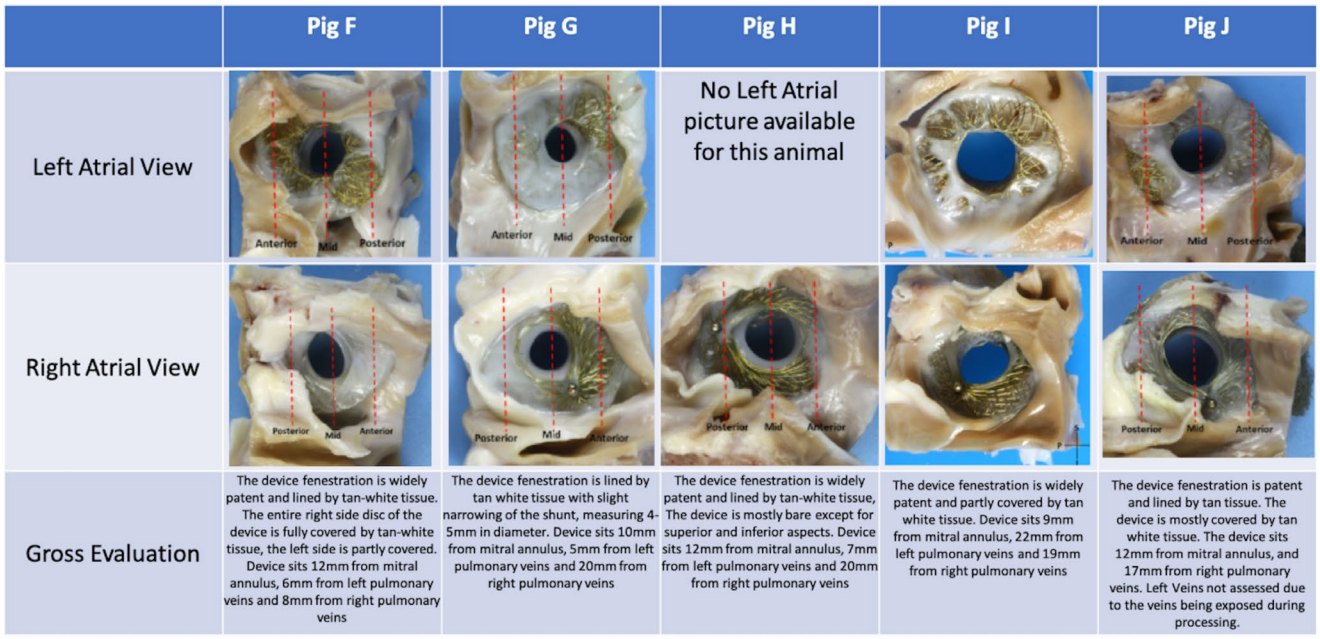


FIGURE 5 Gross evaluation of the AFR in pigs sacrificed at day 90

incorporation greater in areas of device contact with the endocardial surface. The central lumen of each device was patent and showed almost complete coverage of the nitinol struts by mature neointimal tissue along the length of the lumen. The right and the left atrial surfaces of the AFR device showed partial coverage. Focal areas remained bare, notably in areas without clear contact with the underlying septal tissue. Neointimal coverage consisted of minimal granulation tissue with areas of smooth muscle cells proliferation, minimal residual fibrin, and proteoglycan matrix (healing score of 4) (Figure 5).

3.3 | Histology

3.3.1 | Pigs sacrificed at 28 days

Pigs A, B, D, and E were chosen for histology. Pigs A, B, and E all had patent septums. These devices had evidence of endothelization with minimal inflammation and no evidence of thrombus formation (Figure 6). When the device was well opposed to the atrial wall there was better incorporation of neoendocardial tissue (more detail can be found in Table 4). Pig D was seen to have complete occlusion of the lumen. Histologically there was a film of neointimal coverage consisting of granulation tissue, with focal areas of smooth muscle cells some fibrin and proteoglycan matrix. This is consistent with the implantation within the PFO with septal tissue covering the device.

3.3.2 | Pigs sacrificed at 90 days

Pigs F, G, H, and J were selected for histology. In all these pigs, the devices were symmetrically placed and well seated. There was evidence of more endothelialization with neoendocardial tissue, than seen in the pigs at 28 days (Figure 7). Again, the inflammation was low and there was no evidence of thrombus seen. There was minimal inflammation seen and mostly made up of chronic lymphohistiocytic infiltration, scattered hemosiderin-laden macrophages, and occasional giant cells around the wires. In all devices at 90 days, the lumen stayed patent (For more detail see Table 5).

3.4 | Scanning electron microscopy

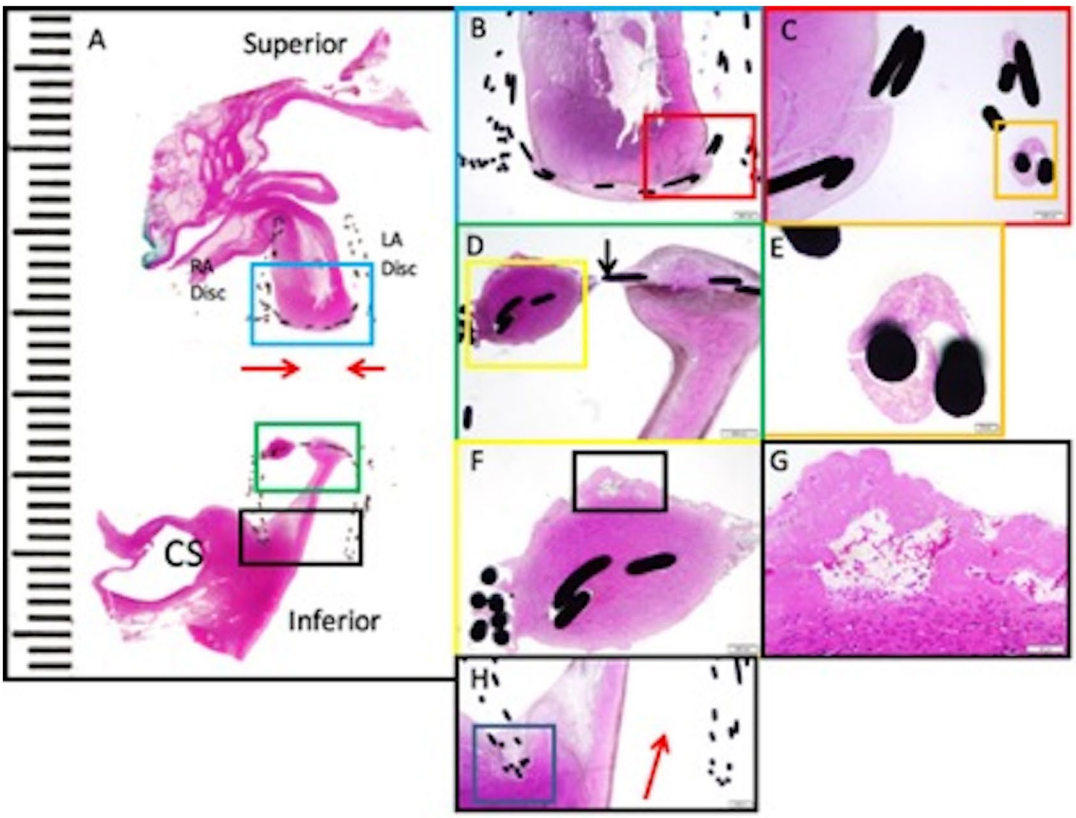
One animal from each group (Pig C and Pig I) was randomly selected for scanning electron microscopy of the device; hence on animal from each group did not have gross or histological examination in order to prepare the specimen for microscopy.

3.4.1 | Electron microscopy at 28 days

This showed the device nitinol wires being partial covered by neoendocardial tissue at the cranial and caudal edges in contact with the atrial endocardial surface. A few of the nitinol wires were surrounded by blood clot consisting of mostly platelets with focal inflammatory cells and fibrin strands. The lumen was widely patent with the device struts here completely covered with surface endothelialization. A few scattered inflammatory cells and platelets adhering to inter-endothelial junctions were also observed. The lumen of the device was minimally reduced secondary to neoendocardial tissue overgrowth (Figure 8).

3.4.2 | Electron microscopy at 90 days

Both right and left sides of the device show multifocal tissue overgrowth on their surfaces, with tissue growth and endothelial cell coverage around the lumen opening on both sides. There is nearly



Histology at Day 28 of Pig A. A. Longitudinal whole mount section of Atrial Flow regulator and atrial wall through the region of the tunnel (left, red arrows) created by the atrial shunt device. The tunnel is fully patent. The device is well seated with the arms of the right disc malapposed at the left side, cranial and caudal aspect, with a gap between the septal wall and the device (H, red arrow); the right aspect is partially apposed to the wall with the flanges in direct contact with the wall. Struts embedded in the cranial and caudal rim of tunnel on the right side are covered by mature neoendocardial tissue (H, blue box); the left arms remain bare. The wires crossing the tunnel are covered by neoendocardial tissue on the cranial aspect (B, C), with the caudal region partially covered with focal areas remaining bare (D, black arrow); platelet-rich and fibrin surface thrombus is observed (F, G). The scale is in mm. All sections stained with Hematoxylin & Eosin stain; RA=right atrium, LA=left atrium, LV=left ventricle, AML=Anterior mitral leaflet, CS= Coronary sinus).

FIGURE 6 Histological assessment of Pig A

complete incorporation of the cranial and caudal aspects of both discs by neoendocardial tissue. The device is well-seated with intact frame and minimal decrease in the lumen. Sequential magnifications of the left- and right-side disc surfaces show endothelialized endocardial overgrowth of the discs as well as at the luminal surface of the device. The majority of the device was free from thrombus, with only one area of the left disc seen with a minute thrombus (Figure 8).

3.5 | Other major organ evaluation

At both day 28 and day 90, organ evaluation showed no significant pathology, without evidence of distant embolization. There was no evidence of significant thrombogenicity or distal embolization. No other major organ demonstrated any significant adverse effects or signs of end organ damage.

TABLE 4 Histological evaluation of pigs sacrificed at 28 days

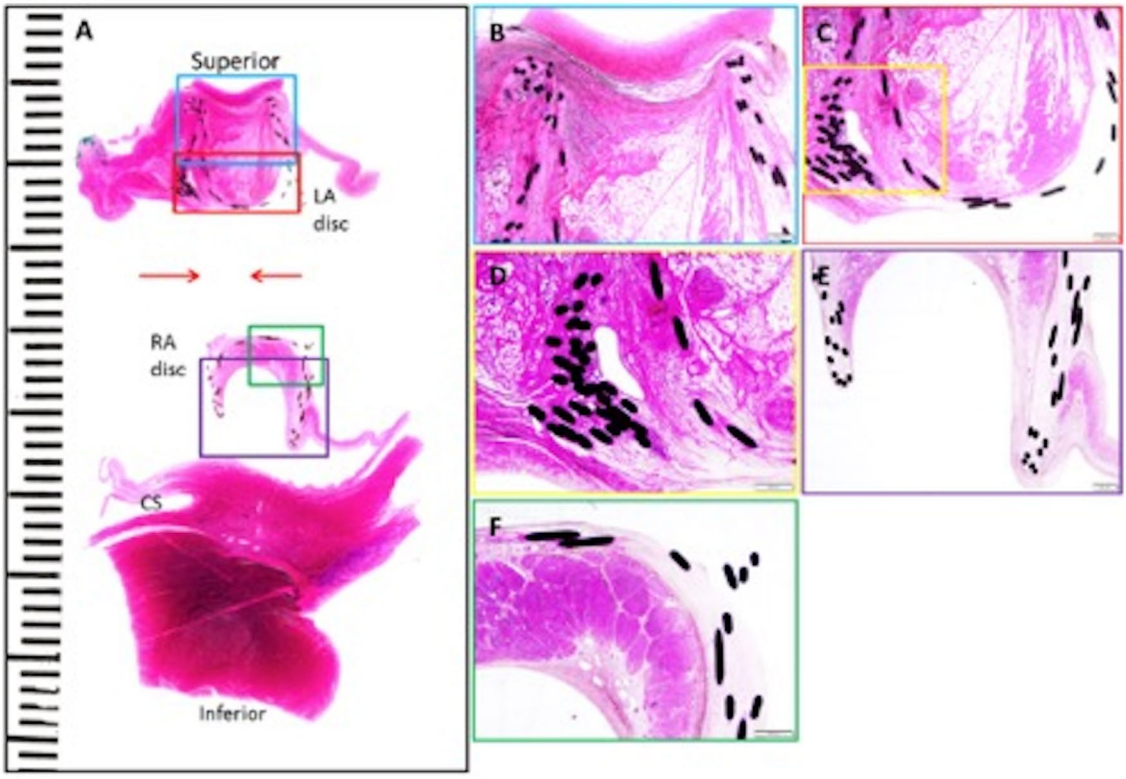
Pig A	Pig B	Pig D	Pig E
• The AFR was symmetrically placed with discs on each side of septum. • Neoendocardial tissue was seen incorporated into the left disc. • The right disc was bare anteriorly with limited healing as it was not touching the underlying atrial wall. • The right disc posteriorly was well seated with neoendocardial tissue overgrowth. • There was no fibrin deposition on either disc. • Inflammation was limited to less than 25% of surface on both sides and consisted of chronic circumscribed granulomatous-like lymphohistiocytic infiltration and occasional giant cells. • The septal tunnel was fully patent. • The device was covered with mostly organizing granulation tissue with minimal chronic inflammatory infiltrates	• The AFR was symmetrically placed and well-seated. • There was a wide gap between the LA disc and atrial septum. • The left disc had minimal tissue growth as it was not opposed to the atrial wall. • There was neoendocardial tissue on both sides of the device, with the struts surrounded by granulation tissue with early focal organization. • There was no fibrin seen on the device. • Inflammation limited to less than 25-50% and limited to chronic, circumscribed granulomatous-like lymphohistiocytic infiltration and occasional giant cells. • Focal subendocardial scarring was present and felt secondary to focal compression of the device on the wall. • The septal tunnel remained fully patent.	• There was complete closure of the AFR orifice. • Histologically there was a film of neointimal coverage consisting of granulation tissue, with focal areas of smooth muscle cells some fibrin and proteoglycan matrix (healing score of 1). • Surface blood clots, consisting of a mixture of fibrin and platelets, were observed within the areas of the mesh but this was an infrequent finding. • The inflammatory response was overall mild (scores 1-2), chronic in nature, composed of lymphocytes, histiocytes and occasional multinucleated giant cells around struts, similar in both the right and left atrial surface	• The atrial flow regulator appeared symmetrically placed and well-seated in the atrial septum. • Flanges are mostly well-opposed to the septal wall on the RA disc, with malapposition observed on the left side with a wide gap between the LA disc and the underlying septum. • The nitinol wires are partially incorporated by neoendocardial tissue on the right side. • The left side shows limited healing as the device was not touching the underlying atrial wall. • The Atrial Flow regulator through the region of the tunnel created by the atrial shunt device shows the device well seated, with a narrowed lumen but patent. I • nflammation is focally mild. • There is no fibrin or thrombus seen on either disc surface.

4 | DISCUSSION

This study has shown that in animal models the AFR is safe, with a standard implantation technique in keeping with the Occlutech range of devices.[6] The creation of an atrial communication is a procedure which is already indicated in patients with pulmonary hypertension or left atrial hypertension, therefore implanting such a device does not add any significant complexity or risk to the standard course for these patients. The implantation of Occlutech-fenestrated ASD devices has already shown to be beneficial at improving PH patients while leaving a defined fenestration that allows for atrial level shunting when required (Joe and Gareth paper).

The pathologic evaluation of the devices demonstrated that there was minimal inflammation seen secondary to the device. The devices were all well seated with evidence of neo-intimal proliferation to secure the device in position. The device does not appear to be thrombogenic with no large thrombus seen and no end organs showing signs of distant emboli shedding. The device discs are small and in all animals, the device was well-centered and not near any other major structures within the heart, specifically it was well clear of the mitral and tricuspid valve, as well as not being in a position that would be concerning for erosion.

At 90 days, the device was not fully endothelialized in any of the pigs. This may be secondary to the fact that the pig atria is smaller than a human atrium for which it was designed. Also the pig atrial septum is thicker and more muscular than a human atrium. This degree of musculature may not have allowed the device to conform to the septum as it would in a human. It was shown that the portions of the discs well opposed to the atrial septum were endothelialized, and those portions without apposition were not covered with the neoendothelial tissue.



Histology at Day 90 of Pig F. Image A shows a longitudinal whole mount section of Atrial Flow Regulator device and atrial wall through the region of the tunnel (left, red arrows) created by the atrial shunt device. The tunnel is fully patent. The device is well seated with the arms of the left disc focally malapposed at the cranial aspect, with both flanges incorporated by tissue growth (Image B). The wires crossing the tunnel are mostly covered by neoendocardial tissue (Images C, D, E), with few struts remaining bare (Image F). The scale is in mm. All sections stained with Hematoxylin & Eosin stain; RA=right atrium, LA=left atrium, CS= Coronary sinus).

FIGURE 7 Histological assessment of Pig F

Pigs have been used for many years as models for medical research and particularly for ASD research.[7] Despite this, there are significant differences between porcine and human atrial septal geometry and structure. It is disappointing but not surprising, therefore, that one animal showed complete obliteration of the orifice of the AFR. This may be in part related to exuberant neointimal growth in a juvenile animal with a highly muscular interatrial septum. This type of response in humans is highly unlikely to occur because the interatrial septum is a mostly membranous structure. Perhaps, also, the patient population that this device is designed for, ie, those with a significant pressure difference between the atriums, driving continuous flow through the device may maintain patency over a device placed between 2 atriums without pressure driven flow. Likely to be more relevant in this case is that the procedure during which this particular device was placed was not straightforward. After a difficult transseptal puncture and device placement, there was no flow on echocardiography prompting us to re-cross the densely occluded central lumen with a septal needle to allow ballooning of the lumen. The occlusive tissue was so dense that it lead us to postulate that the device had been deployed within the tissue of the septum rather than on either side.

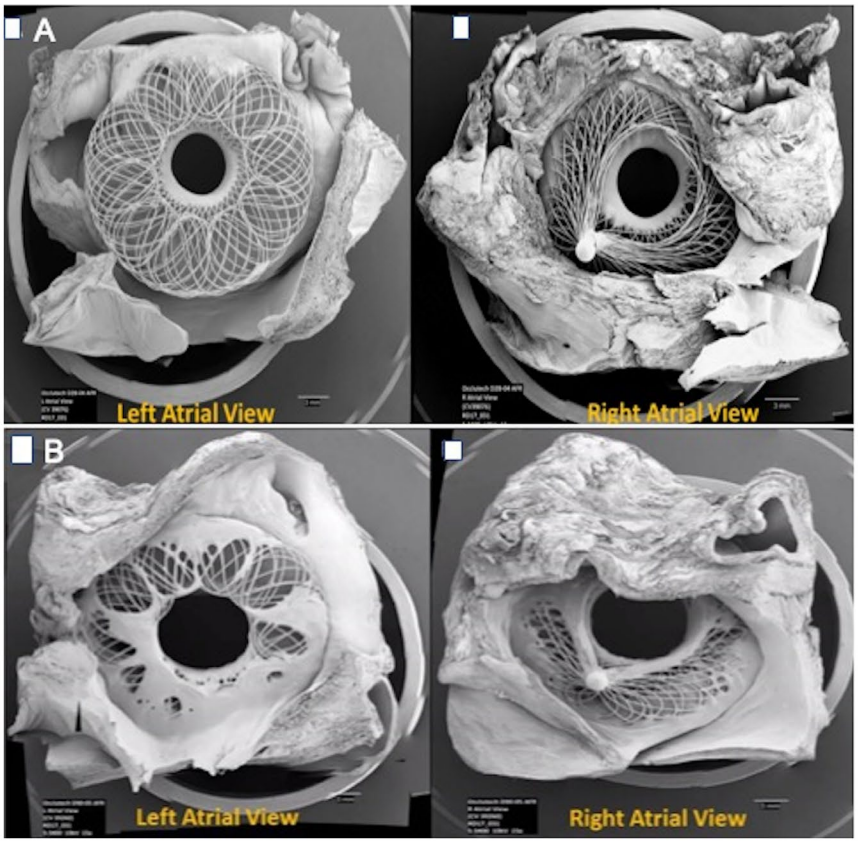
When this animal's histology was further examined, it showed dimpling on the right side of the central occlusion but smooth tissue on the left side. The tissue appeared to have a laminated appearance extending out from the center suggesting circumferential encroachment as with a closing diaphragm. The left side was also seen to have a more florid tissue reaction and some features of ossification. This is very unusual to see in porcine hearts and although reported in other animals has not been described in pigs. It has been seen in human valve histology, that the calcification of the valve, can have the presence of woven-bone tissue.[8] This pathological process may also be able to occur within the heart in the right circumstance.

TABLE 5 Histological evaluation of pigs sacrificed at 90 days

Pig F	Pig G	Pig H	Pig J
• The device is symmetrically placed, well seated with the right disc well opposed to the atrial wall. • The right atrial disc is almost fully covered by neoendocardial tissue. • The left disc due to its incomplete apposition has less neoendocardial coverage. • There is no surface fibrin deposition on either side of the device. • Granulation tissue and inflammation are minimal. • Inflammation is limited to less than 25% of surface on both sides and consists of chronic lymphohistiocytic infiltration, scattered hemosiderin-laden macrophages, and occasional giant cells around the wires. • The device lumen is fully patent.	• The Atrial Flow Regulator appears symmetrically placed, well-seated. • Both aspects of the device show focal malapposition caudally to the underlying atrial septal wall. • The left side is mostly covered while the right disc shows partial coverage. • The device lumen is fully patent. • Granulation tissue and inflammation are minimal. • There is no surface fibrin deposition on either side of the device. • Inflammation is limited to less than 25% of surface on both sides and consists of chronic lymphohistiocytic infiltration and occasional giant cells around the wires.	• The Atrial Flow Regulator appears symmetrically placed, well-seated, with the right disc well-opposed to the underlying atrial septal wall. • The left disc is not fully apposed at its most cranial extent. • The device lumen is fully patent. • The right disc is incorporated by thin neoendocardial tissue, with the left disc partially covered by tissue where the disc is apposed to the septum. • Granulation tissue and inflammation are minimal in this section. • There is no surface fibrin deposition on either side of the device. • Inflammation is limited to less than 25% of surface on both sides and consists of chronic lymphohistiocytic infiltration and occasional giant cells around the wires	• The atrial flow regulator appears symmetrically placed, well-seated with both aspects of the device well-opposed to the underlying atrial septal wall. • The right flange is mostly incorporated by neoendocardial tissue, with parts of the disc covered by thin neoendocardial tissue growth, with few of the most superficial struts remaining bare. • The left disc is mostly covered with few struts remaining bare. • The device lumen remains fully patent. • Granulation tissue and inflammation are mild. • There is no surface fibrin deposition on either side of the device. • Inflammation is limited to less than 25% of surface on both sides and consists of chronic lymphohistiocytic infiltration, scattered hemosiderin-laden macrophages and occasional giant cells around the wires.

In another pig, the device had embolized within 24 hours. This pig had a significant PFO which, within the small porcine septum, confounded attempts to perform a separate transeptal puncture. Therefore, the device was deployed across the PFO. As with many other clinical correlates where performing a dedicated transeptal puncture is preferable over crossing a PFO; the stability of a device with a design such as the AFR may not be optimal without a septal puncture. In this study, once the pigs are anesthetized, it will be included in the study and euthanized. Therefore, the device was implanted and later embolized to the descending aorta. Further work with human modeling will be needed to determine the suitability of PFO anatomy which may allow safe deployment in such a circumstance.

One question not answered by this study is how large a fenestration to aim for in each individual patient. This device in theory could be used in almost all age groups, including in pediatric patients with congenital heart disease. The volume of flow across a fenestration is affected by pressure gradient, viscosity of the blood, and body surface area among others. We propose that using Poiseuille's law (see Appendix 1) allows us to quantify the volume of blood flowing through the device.[7] The relative viscosity of blood with a hematocrit of 40 to 45 is between 2.5 and 4, we used 3 as our viscosity at 37°C and hematocrit of 45. For every 4.8 rise in hematocrit, the viscosity increases by 1 unit.[9,10] This allows us to calculate the flow across the shunt using the measured pressure gradient and in each different available length and diameter of AFR (length is either 2, 5, or 10 mm, and diameter is either 6, 8, or 10 mm). Using the Fick equation or thermodilution (Appendix 2) to estimate the pulmonary blood flow, we can determine or at least estimate the most appropriately sized device to allow for an appropriate drop in systemic saturations (Appendix 3). Further studies and experience with this device will be required to predict the ideal fenestration size for each patient.



Picture A) - Scanning electron microscopic composite views of the right and left Occlutech atrial flow regulator device at Day 28. Both right and left sides of the device show minimal tissue overgrowth on their surface, with tissue growth and endothelial cell coverage around the tunnel region on both sides. There is focal incorporation of the cranial flange of the left disc at its contact point with the septal surface and within the peripheral nitinol wires of the right side. The device is well-seated with intact frame. Both images at 15X.

Picture B)- Scanning electron microscopic images of the right and left aspects of the Occlutech Atrial Flow Regulator device at 90 days. Both right and left sides of the device show multifocal tissue overgrowth on their surfaces, with tissue growth and endothelial cell coverage around the tunnel region on both sides. There is mostly incorporation of the cranial and caudal flanges of both right and left discs by neoendocardial tissue growth, as they are in direct contact with the underlying atrial septal surface. The device is well-seated with intact frame. Magnification for both images at 15x.

FIGURE 8 EM of Pig C at 28 days and Pig I at 90 days

5 | LIMITATIONS

There were several limitations with this study. As already stated, the atrial anatomy and atrial septum in pigs are morphologically different from humans, smaller, and more muscular. Another limitation is the physiology of the healthy pig models. This device is designed to be used in patients with high atrial pressure gradients; the pigs in this study were healthy and unlikely to have a high gradient. Another limitation was that the number of devices implanted was small. Only 11 devices were implanted, more implantations would better help show the safety and efficacy of the device.

6 | CONCLUSION

PAH and left ventricular diastolic dysfunction are diseases with significantly associated morbidity and mortality.[6,11] There is good evidence that the creation of an atrial communication can reduce this associated morbidity and mortality.[1-3] The Occlutech AFR has shown to be safe and easy to implant with good results.[3] This study has further shown that histologically the device does not cause any end organ damage, causes minimal inflammation, with almost no thrombus formation and can remain patent, and secure in the atrial septum. This device can be very effective in creating a predictably sized atrial communication that may improve symptoms and reduce morbidity and mortality in patients with PAH, left ventricular diastolic dysfunction, and congenital heart disease. This information should contribute to a wider understanding of expectation for human efficacy with the AFR.

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CONFLICT OF INTEREST

Dr. Morgan is a consultant for Occlutech.

AUTHOR CONTRIBUTIONS

DM was responsible for the writing of the body of the article. GM as senior author responsible for the design and review of the article as well as significant contribution to the writing of the introduction and methods. DI was responsible for the information on pulmonary hypertension, review of the article and changes as required.

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APPENDIX 1.

Poiseuille's law

$$V = \frac{\pi \Delta p r^4}{8 \eta l}$$

V = Flow rate, p = Pressure gradient, r = radius, l = length, η = Viscosity.

APPENDIX 2.

Fick principle

$$Q_p = \frac{VO2}{0.136 \times Hb \times (PVO2 - PAO2)} (L/min/m^2) \quad (1)$$

Q_p = pulmonary blood flow, VO_2 = the oxygen consumption (adjusted for each patient per the Sekeller table), PAO_2 = pulmonary arterial oxygen saturation (ie, 99% = 99 in the equation), PVO_2 = pulmonary vein saturation.

APPENDIX 3.

Example

Patient X is 10-year-old male with a HR of 90 bpm, weight of 30 kgs, and height 150 cm. He has a Hct of 45, hemoglobin 15, right atrial pressure of 10, a left atrial pressure of 7, mixed venous sat of 70%, and pulmonary vein saturations of 100%. For AFR sizing, first calculate the baseline Qp:

$$Qp = 149/(15 \times 0.136) \times 30 = 2.43\,L/min/m^2$$

A shunt of 0.5 L/min/m^2 across the atrial septum would give systemic saturations of 93.8%, this is because the Q_p would reduce to 1.93 L/min/m^2 with 0.5 L shunting across the septum. Therefore, with 1.93 L/min having 100% saturation and 0.5 L having 70% you add 1.93 × 100 and 0.5 × 70 and then divide by 2.43.

By Poiseuille's law with knowing that the flow must be 0.5 L/min/m^2 which adjusted for BSA = 0.56 L/min. The device length is 5 or 10 mm, using 5 mm and a diameter of 6 mm gives a Q_p of 0.51 L/min. which accounted for BSA is 0.46 L/min/m^2. Using the above formula that would give a systemic saturation of 94.3%.