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Improvements in the cuff and graft interface with a Total Artificial Heart

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ABSTRACT

Research Question: Our initial question was: are there TAH-graft interface irregularities which could lead to blood flow disruption?

Introduction and Significance: Our objective was to evaluate design improvements of the inlet cuff-port and outlet graft-port interface of a Total Artificial Heart (TAH) on pannus formation. The orifice size, interface, blood flow path geometry, blood flow velocity, materials, surface finish, and hematologic parameters (such as anti-coagulants and anti-platelets) all contribute to the hemocompatibility of the TAH inflow and outflow. The focus of this work is the blood flow path geometry and material change. Practical application of this research involves progression of TAH as a method of treatment of potentially definitive treatment of heart failure, and as an extended bridge therapy until heart transplantation.

Materials and Methods: The performance of progressive inflow and outflow design iterations of a rotary total artificial heart operated in continuous and pulsatile outflow were evaluated in Corriente calves for durations of 30 days. Design modifications included a smoother blood flow port transition, geometrical improvements to the diameter and tangent angle to the polyurethane connector/pump interface, and methods of securing the connection including a titanium ring on the cuff with biospan rings and PEEK zip ties on both the cuffs and grafts. The graft flow path includes a circumferential hump which allows the titanium outflow port to seat against this hump and eliminate a void which could be a source of thrombus or emboli. Additionally, the cuff and port materials were changed. Subjects were 6-12 month old calves with weights ranging from 82 kg to 108 kg, while conditions such as pump flow, pressures and anticoagulants were closely monitored. The TAH was run in pulsatile mode for most of the studies. At necropsy, photos of the cuff and graft interface to the pump were analyzed and any tissue samples were sent for histological evaluation.

Results: A titanium ring on the cuff prevented the cuff from pulling away from the titanium port at the ostium and prevented the cuff from being pulled too far onto the port during surgical installation. Pannus formation at the interface of the cuff and graft to the titanium ports was graded from Absent (0) to Extreme (5), (Extreme equals >75% area reduction). In earlier design iterations, pannus formation at the inflow cuff or outflow graft interface ranged from (2) mild to (5) extreme. After implementing the design improvements, pannus was (0) absent in all inflow cuff interfaces. One graft that was not fully installed on the port had moderate buildup and the remainder had (0) absent to (1) minor at the outflow graft interface despite minimal anticoagulation.

Conclusions: Improvements to the inflow cuff/outflow graft-port interface significantly reduced pannus and thrombus formation in chronic animal implants treated with limited anticoagulation.

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RESEARCH QUESTION

Our initial question was focused on the investigation into TAH-graft interface irregularities which could lead to blood flow disruption. We utilized reproduction rubber studies to evaluate margins of error in the manufacturing process that led to reduced interface gaps.

INTRODUCTION AND SIGNIFICANCE

Congestive heart failure (CHF) is a highly prevalent diagnosis within the United States. Estimates pin overall disease burden at impacting 6.2-million individuals, which translates to 2.2% of the overall population^[1]. The medical treatment of this condition largely focuses on preservation of ventricular function with progressively intensive treatments according to either the patient's American Heart Association (AHA) or New York Heart Association (NYHA) classifications. Management & treatment begins with relatively benign interventions such as lifestyle changes, weight loss, reduction of substance ingestion, and proper management of other health conditions; this can be considered stage A, with a goal of primary prevention. Interventions, however, will increase pharmacologic management depending upon classification level and patient tolerance. Per the AHA guidelines, stage dependent pharmacotherapy includes^[2]: stage B- angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), beta blockers (BB); stage C- aldosterone antagonists, loop or thiazide diuretics, isosorbide dinitrate / hydralazine, angiotensin receptor-neprilysin inhibitors (ARNIs), SGLT2 inhibitors; stage D- inotropic support, transplants, other invasive interventions.

The TAH is largely utilized as an end-stage intervention only as a last line, often after patients have failed LVAD interventions^[2]. The AHA guidelines recommend surgical interventions as stage-D, once patients are in the terminal stage with confinement to bedrest and discomfort with any level of physical activity^[2].

Our objective is to build on previous TAH research that has been performed with the Jarvik models. This previous study showed that optimal cuff material was Biomer which resulted in a rate of pannus formation in 17% of study calves^[3]. Modern cuff materials that were utilized in this study consisted of polyurethane internally and velour as a surface finish. The subject of study for this paper is primarily focused on the design improvements made to the inlet & outlet cuff-port interface such that a significant reduction in pannus formation is achieved. Historically, this region is highly susceptible to turbulence & pannus formation^[4].

MATERIALS & METHODS

Initial subjects consisted of 5 Corriente calves sourced from with weight at implantation of the TAH ranging from 82kg to 108 kg. Table 1 shows pertinent data for the 5 subjects. Animals were raised in a standardized manner, receiving comparable amounts of caloric intake, medications, and supervision prior to implantation.

Subject	DOB	Implant date	Study duration (Days)	Weight at implant (Kg)	Weight at term (Kg)	Cause of Termination
B-2064	June-2021	03, May-2022	30	103	86.1	Elective
B-2070	June-2021	12, Jul- 2022	30	93.6	101.4	Elective
B-2067	June-2021	03, Aug- 2022	30	105.9	115.2	Elective
B-2079	Aug-2021	16, Aug- 2022	30	108	94.3	Elective
B-2080	Aug-2021	07, Sep- 2022	30	81.8	80.7	Elective

Table 1- Displays data pertinent for subjects on DOB, weight changes during study cause of termination, and implantation length as well as duration.

These animals were maintained in a controlled environment, with some receiving anticoagulation therapy. Subject B-2064 received 100-600u heparin/hr starting on POD 1, as well as Warfarin starting on POD 03-08 with INR titration to an objective of 1.8 ± 0.9 . Subject B-2070 received 500u heparin/hr on POD 22 and onwards. All other subjects did not require anticoagulation post-implantation. Animals were evaluated periodically by physicians/veterinarians with special care to the region of the graft attached to pump power supply cables. Termination of subjects was performed in a humane manner that was compliant with IRB approval and minimized the suffering of the subject. Necropsy was performed by physicians at the Texas Heart Institute.

Graft material consisted of internal surface coating with polyurethane, outer material being velour. Cuff was designed for compliance with the TAH metal barb that allowed the material to be pulled over and secured. Additionally, we elected to utilize a titanium ring around the cuff material to provide security and retain the cuff in place.

The overview of the engineering process to determine the proper mold shape started with measuring the legacy molds, parts from the molds, and the ports. This includes some measurements from a cross-section on the circulatory connections to get an understanding of the shrinkage that occurs during the molding process.

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Ultimately, it was important that before the molds were changed, the circulatory connections were attached to the port to measure the gap it creates at the ostium. Low shrinkage reproduction rubber was then pressed into the parts in order to create a replication of the flow path that could be removed shortly after and then measured. This was done with a combination of 5 different circulatory connections to determine how the parts deformed in order to create an empirical model for mold shrinkage and part deformation. One thing to note is that interference was prescribed at the angular face of the barb. This was done to produce a robust interface that will not expand under pressure as well as give the surgeon a tactile snap that ensured that the cuff/graft is seated properly. Once this empirical model was developed, this was compared against a lot of 50 measurements from the machined ports to estimate how the proposed mold changes will affect the fit. This final step informed the tolerances that the molds needed in order to cover the variances in the port machining. The figure below shows a reproduction rubber study of a part made by the newly proposed geometry changes that was mated to an inflow port. It can be seen that the mismatch was greatly reduced to 17.3 μm and 39.4 μm and the flow would always “Step Up” to prevent any areas of stasis.

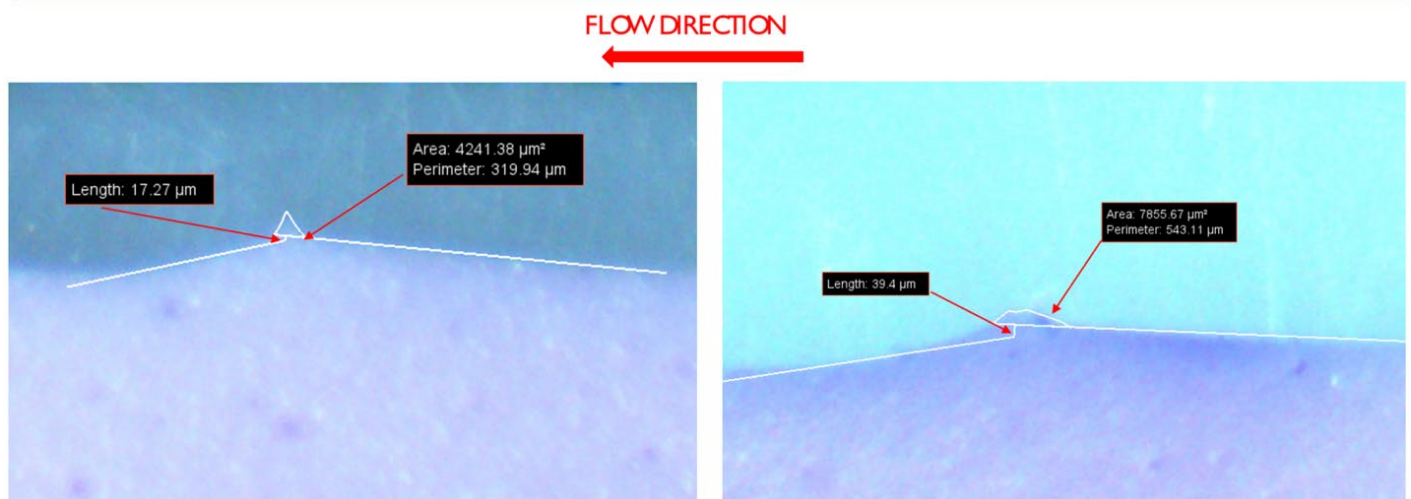


Figure 1. Reproduction Rubber Study of Ostium Interface

In regard to material selection, typically silicones or polyurethanes that are hemocompatible are typically selected for the circulatory connections. The disadvantage of silicones are that they are not as strong or tough as polyurethane, but they are usually more hemocompatible such as NuSil

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Silicone. The polyurethanes as mentioned before are typically much stronger and tougher than the silicones, and they adhere better to the stiffening mesh. DSM is a vendor of these implant grade polyurethanes which come in a few mixtures that have modifiers to improve their properties based on the application. This includes Carbosil, BioSpan F, BioSpan S, and Bionate. Ultimately, BioSpan S, a silicone modified polyurethane was selected based on the additional hemocompatible properties as well as the manufacturability of the material. BioSpan S is suspended in a DMAC solvent to delay the reaction of the polyurethane. DMAC can be added to modify the viscosity of the mixture to allow it flow more easily into tightly woven fabrics to create a strong bond. The prescribed surface finish tolerance on cuff materials to minimize interaction with blood components such as plasma proteins, lipids, and cells themselves is recommended to be below $1\mu\text{m}$ of tolerance^[5], our manufacturing methods produce a surface finish typically between $0.05\mu\text{m}$ & $0.1\mu\text{m}$.

RESULTS

Assessment of inflow and outflow at time of subject termination was performed in an objective and consistent manner that is consistent with the AVMA guidelines on Euthanasia, 2013 and THI SOP-ANI030, *Euthanasia of Research Animals*.

The necropsy was performed as follows:

1. The necropsy was recorded on video as well as by taking photographs.
2. A gross evaluation with photography was performed on the heart, liver, spleen, lungs, brain, kidneys, and any other area of interest. All photographed organs had a ruler in the field of view. Each end organ was weighed following removal.
3. The Percutaneous Driveline Cable was photographed and examined for inflammation and degree of tissue ingrowth.
4. The TAH was examined as follows:
 - 4.1 The atrial remnants and pump were photographed within the chest;
 - 4.2 The atrial remnants were removed with the pump attached, preserving the pulmonary artery, aorta, and corresponding attachments to the pump;
 - 4.3 The Inflow Cuffs were examined and photographed inside of the left and right atria. Any evidence of thrombus formation at this interface were also recorded;
 - 4.4 The pump was removed from the heart and photographed;
 - 4.5 The pump cavity was observed for thrombus formation;
 - 4.6 Once removed, the pumps interface with surrounding tissue was photographed.
5. TAH pump components were examined as follows:
 - 5.1 The outside surface of the pump and any visible aspects of the Inflow and Outflow ports were examined and photographed for evidence of thrombus formation;
 - 5.2 The Inflow Cuffs were disengaged / removed from the Pump Body, next, the Inflow Cuffs were examined and photographed;
 - 5.3 The Outflow Grafts were disconnected from the Pump Body. The connection between the inside surface of the Outflow Grafts and the Pump Body were also examined and photographed for evidence of thrombus formation;

5.4 The Outflow Grafts were examined and photographed at the aortic and pulmonary artery anastomosis sites; they were then dissected longitudinally, examined, and photographed;

5.5 After consultation with the sponsor the following steps were performed at the study facility for certain subjects;

5.5.1 The pump was opened, photographed, and examined;

5.5.2 The Rotor was removed from the pump housing;

5.5.3 The internal surfaces of the right and left sections of the Pump Housings were examined and photographed;

5.5.4 The Inflow and outflow ports were examined and photographed;

5.5.5 The Rotor surface was examined and photographed;

5.6 Following all evaluation, the Outflow Graft was discarded. All implanted test article components, including the Pump Body, Inflow Cuffs, Percutaneous Driveline Cable, were rinsed with saline and returned to the Study Sponsor. The Patient Controller was also spot-cleaned and returned to the Study Sponsor.

6. Additional photographs to those specified above were also obtained at the discretion of the pathologist and were, when taken, included a ruler in the field.

7. Tissue specimens that were collected for processing:

7.1 Tissue specimens were collected for histopathology from the following organs: atria, liver, spleen, lungs, brain (following an appropriate period of fixation), and kidneys;

7.2 Tissue specimens were also collected from inside of the pump (if necessary), and each cannulation/anastomosis site.

Any other suspected areas of interest determined by the pathologist.

We utilized the same grading system as present in the 1981 Jarvik paper^[3]. This yielded absent pannus growth in 4 of the 5 subjects, with the last one only exhibiting minor pannus growth.

Pannus grade	Area Reduction (%)	Lumen Size	Pannus Shelf Size
0- Absent	0%	2.4 cm	0
1- Mild	<25%	2.0-2.4 cm	<2mm
2- Moderate	25-50%	1.6-2.0 cm	2-4mm
3- Severe	50-75%	1.2-1.6 cm	4-6mm
4- Extreme	>75%	<1.2 cm	>6mm

Table 2- Pannus grading system utilized in this study. Same measurements as predecessor Jarvik study^[3]



Figure 2A & 2B: 2A (Left image)- Subject B-2064 L sided inflow cuff. 2B (Right image)- Subject B-2064 R sided inflow cuff.



Figure 3A, 3B, 3C

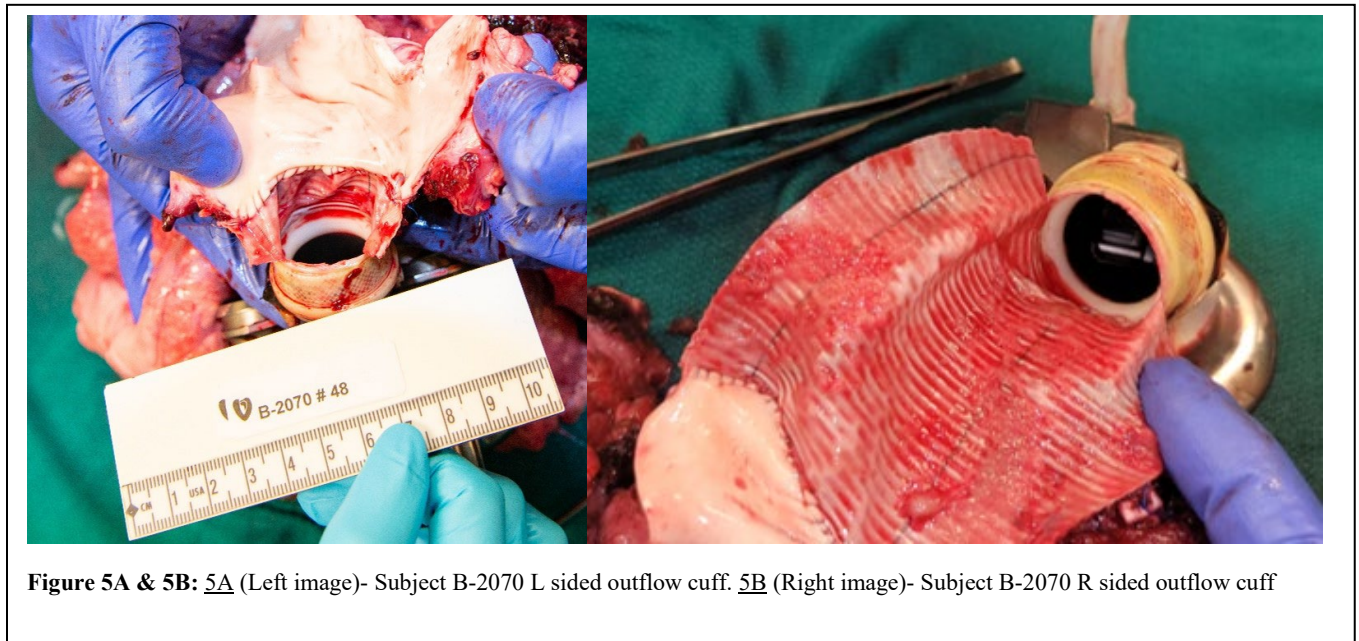
-3A (Left upper image)- Subject B-2064 L sided outflow graft.

-3B (Right upper image)- Subject B-2064 R sided outflow graft.

-3C (Left lower image)- Subject B-2064 R sided outflow graft, alternate view.

Subject B- 2070 -PANNUS RISK: ABSENT

Subject was implanted on July 12, 2022, maintained for 30 days until elective termination. Subject gained 7.8Kg during trial period. There is no evidence of significant pannus growth that was visible on necropsy.



Subject B- 2067 -PANNUS RISK: MILD

Subject was implanted on August 03, 2022, maintained for 30 days until elective termination. Subject gained 9.3Kg during trial period.

Evidence of pannus growth from graft interface (Fig 7A ~4-5 o'clock position) on L sided outflow graft consistent with neo-endothelialization originating from the cuff-barb interface. Visible neo-endothelialization tissue at cuff interface (Fig 7B & 6C) over R sided outflow cuff.

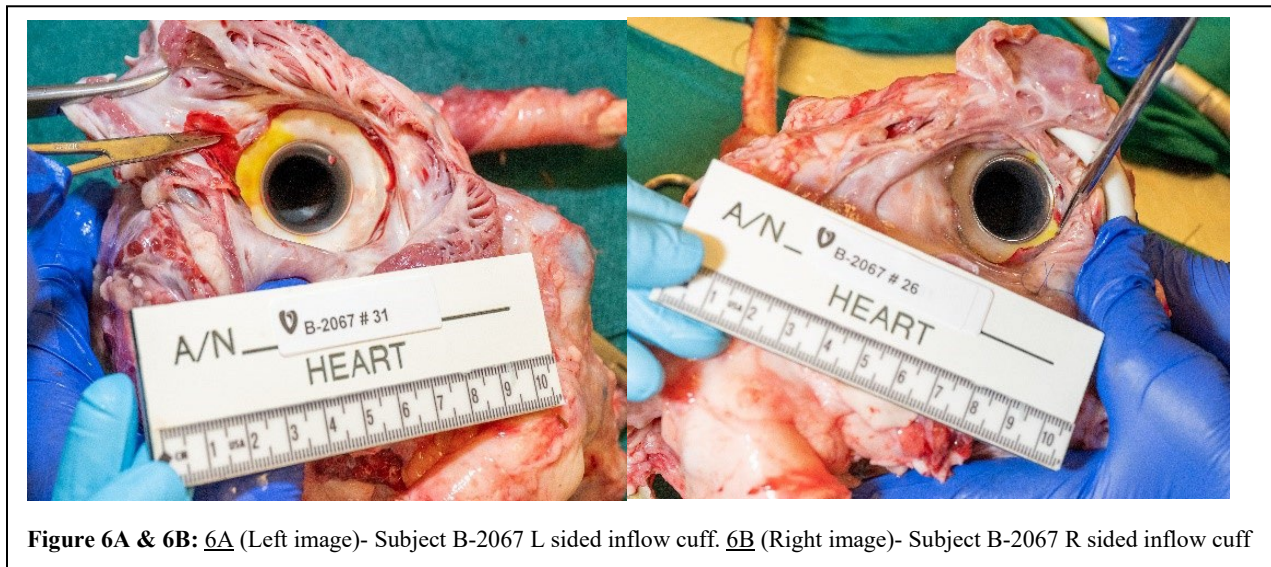




Figure 7A, 7B, 7C

-7A (Left upper image)- Subject B-2067 L sided outflow graft.

-7B (Right upper image)- Subject B-2067 R sided outflow graft.

-7C (Left lower image)- Subject B-2067 R sided outflow graft, alternate view.



Subject B- 2079

-PANNUS RISK: MILD

Subject was implanted on August 16, 2022, maintained for 30 days until elective termination. Subject lost 13.7Kg during trial period.

There is no evidence of pannus growth in either inflow tract for this subject (Fig 8A & 8B). The right sided outflow tract shows no evidence of pannus growth (Fig 9B). Evaluation of Left sided outflow tract showed minimal development of pannus within the subject (Fig 9A & 9C). Evaluation of reference figures shows that the neo-endothelialized pannus is attached minimal distal to the cuff-biological interface with no significant coagulation seen at the point of suture attachment.

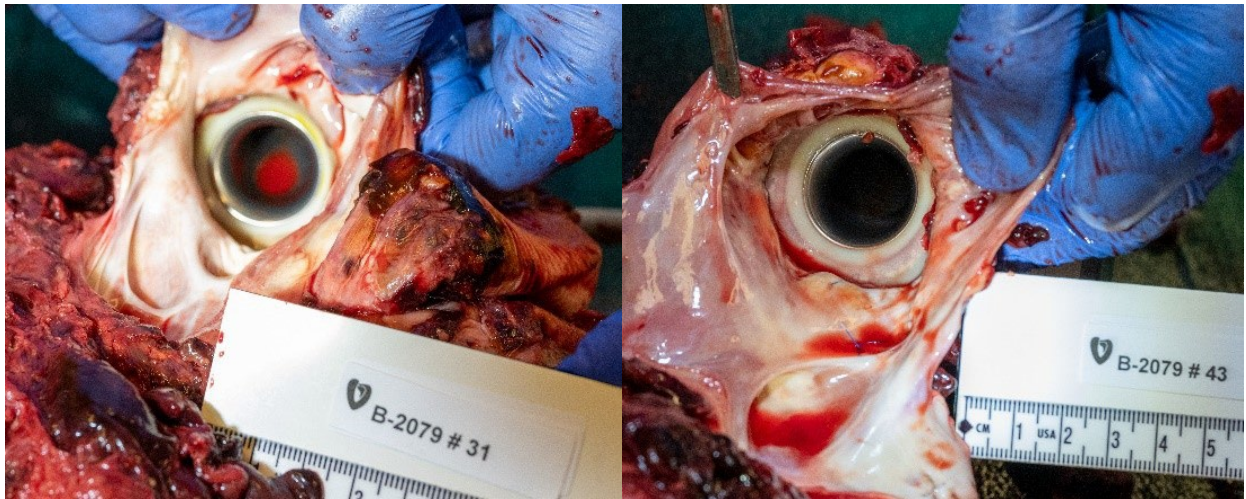


Figure 8A & 8B: 8A (Left image)- Subject B-2079 L sided inflow cuff. 8B (Right image)- Subject B-2079 R sided inflow cuff

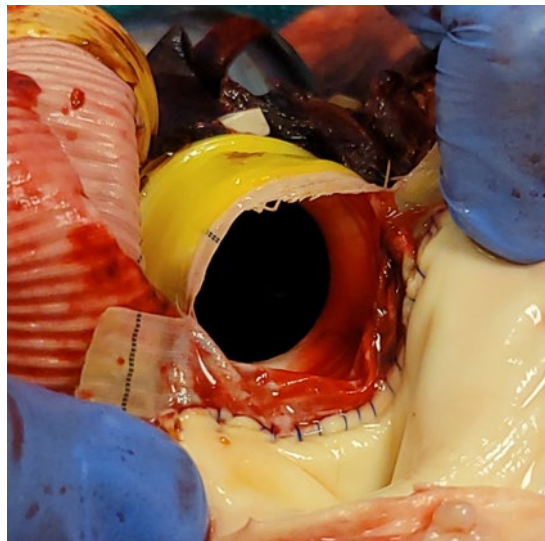


Figure 9A, 9B, 9C:

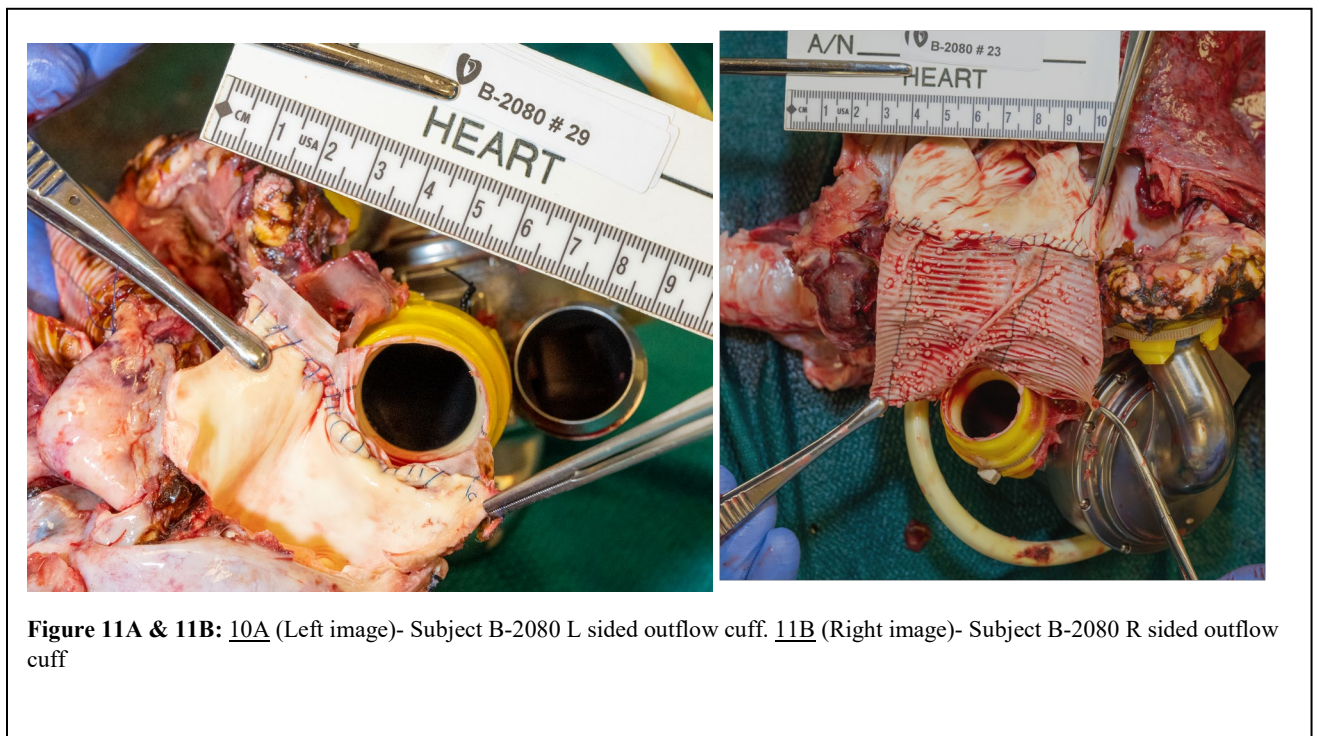
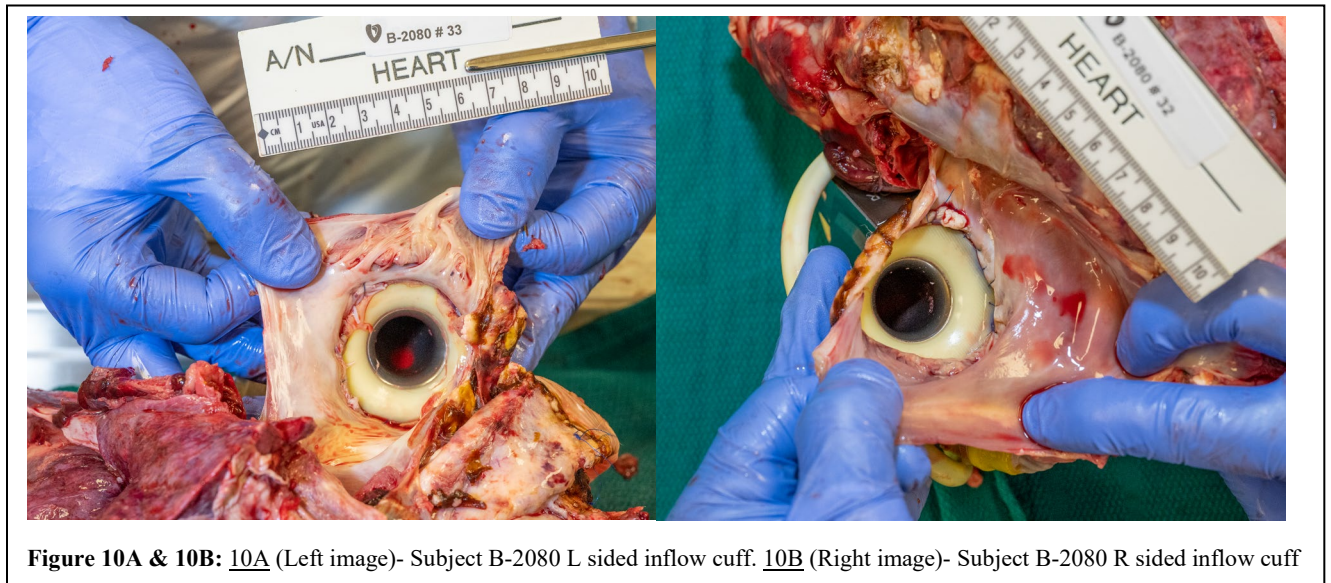
-9A (Left upper image)- Subject B-2079 L sided outflow graft.

-9B (Right upper image)- Subject B-2079 R sided outflow graft.

-9C (Left lower image)- Subject B-2079 L sided outflow graft, alternate view.

Subject B-2080 -PANNUS RISK: ABSENT

Subject was implanted on September 07, 2022, maintained for 30 days until elective termination. Subject lost 1.1Kg during trial period. There is no evidence of significant pannus growth that was visible on necropsy.



DISCUSSION

Overall our approach to cuff development has yielded significant improvements in pannus growth and subject survival. Continuing the previous development of artificial hearts in the realm of bovine subjects will continue being an important steppingstone to human trials. Further modification on TAH power delivery systems and anticoagulation regiment would be areas of development that could pave a path toward increased implantation rates alongside increased patient mobility. Our specific characteristics of an internal surface coating with polyurethane and outer material being velour created a combination of minimal thrombogenicity while simultaneously maintaining structural integrity that would be required for extended implantation periods.

The approach for human subject studies would involve appropriate subjects that exhibit appropriate physiologic capacity to undergo surgery. Often the difficulties involved with TAH patients is that by the time of acceptance for implantation the patient has deteriorated to such a marked clinical degree that signs of improvement are minimal at best. A vital consideration involves a fragility index to guide patient selection, as a higher index will portend poor patient outcomes. The number one risk factor for complications post-TAH transplantation is smoking^[6]. A multi-institutional study by WL Holman Et Al. found that there were key clinical risk factors associated with patient mortality. The found factors included age, ascites, increased bilirubin levels, and INTERMACS Level 1^[7]. While the findings in this study primary included assist devices vs TAHs (396 vs 24) the concerning factors can nonetheless be applied to our future studies.

Further research would be aimed at evaluation of pannus growth within the cuff-biologic interface. While ensuring smooth convergence at the cuff-barb level has been shown in this paper to be a significant factor in controlling for pannus presence. The surface finish of the graft itself is of little concern as we were able to attain finish levels an order of magnitude lower than those ordinarily prescribed^[5] ($0.05\mu\text{m}$ - $0.1\mu\text{m}$ vs $1\mu\text{m}$). The other point of interface may still reveal potential causes of embolic events.

FUTURE DIRECTIONS

The future of artificial hearts holds great promise as technological advancements continue to reshape the landscape of cardiovascular medicine. Currently BiVACOR has submitted for first in human trials with the FDA and received approval. In the coming years we can anticipate further studies & developments advancing utilization of this technology.

One further prominent avenue of exploration involves the integration of artificial intelligence (AI) and machine learning algorithms to enhance the functionality and adaptability of artificial hearts. By leveraging real-time patient data, these systems could optimize pump performance, anticipate physiological changes, and customize the heart's response to varying demands. This personalized approach may lead to improved patient outcomes, reduced complications, and increased longevity of artificial heart devices.

Furthermore, the development of supplementary biocompatible materials and advanced manufacturing techniques offers another exciting trajectory for artificial heart evolution. Innovations in materials science, such as the use of bioengineered tissues and nanomaterials, aim to create more durable, efficient, and responsive artificial hearts. The integration of smart materials that can respond dynamically to physiological cues may mimic the intricate functions of a natural heart more closely. As research continues to push the boundaries of bioengineering and materials science, the next generation of artificial hearts may not only sustain life but also adapt seamlessly to the complexities of the human cardiovascular system, ushering in a new era of cardiac care and transplantation.

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CONCLUSION

Our studies of material, manufacturing, and biologic graft success bode well for future development of TAH implementation within humans. The low utilization of anti-coagulation therapies, maintenance of TAH barb patency, and minimal complications of experimental subjects point toward successful minimization of thrombogenic conditions within the graft interface.

COMPLIANCE

All subject studies were approved by IUCAC at Texas Heart institute.

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