Cavopulmonary assist: long-term reversal of the Fontan paradox

Short title: Cavopulmonary assist for long-term Fontan reversal

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Article word count: 3485/3500

Supported in part by National Institutes of Health Bioengineering Research Grant R01 HL098353, Big Hearts to Little Hearts, Children's Heart Foundation, Matthews Hearts of Hope.

Presented at the 99th Annual Meeting of the American Association for Thoracic Surgery, May 6, 2019.

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Structured Abstract:

Objective: Fontan circulatory inefficiency can be addressed by replacing the missing subpulmonary power source to reverse the Fontan paradox. An implantable cavopulmonary assist device is described that will simultaneously reduce systemic venous pressure and increase pulmonary arterial pressure, thereby improving preload and cardiac output, in a univentricular Fontan circulation on a long-term basis.

Methods: A rotary blood pump based on the von Karman viscous pump was designed for implantation into the total cavopulmonary connection (TCPC). It will impart modest pressure energy to augment Fontan flow without risk of obstruction. In the event of rotational failure, it is designed to default to a passive flow diverter. Pressure-flow (H-Q) performance was characterized *in vitro* in a Fontan mock circulatory loop using blood analog.

Results: The pump performed through the fully specified operating range, augmenting flow in all 4 directions of the TCPC. Pressure rise of 6-8 mmHg was readily achieved, ranging up to 14 mmHg at highest speed (5600 RPM). Performance was consistent over a wide range of cardiac output. In the stalled condition (0 RPM), there was no discernible pressure loss across the TCPC.

Conclusions: A blood pump technology is described that can reverse the Fontan paradox and may permit a surgical strategy of long-term biventricular maintenance of a univentricular Fontan circulation. The technology is intended for Fontan failure in which right-sided circulatory inefficiencies predominate and ventricular systolic function is preserved. It may also apply prior to clinical Fontan failure as health maintenance to preempt the progression of Fontan disease.

Abstract word count: 249/250

Central Message: An implantable blood pump that can safely and reliably reverse the Fontan paradox long-term may enable a physiologically curative strategy for single ventricle heart disease. (Characters including spaces: 174/200)

Perspective Statement: Fontan palliation is associated with a chronic circulatory inefficiency that culminates in secondary disease, failure, and attrition. We report feasibility of an implantable cavopulmonary assist device that can safely replace the missing subpulmonary power source and reverse the Fontan paradox long-term. This may enable a physiologically curative strategy for single functional ventricle. (characters including spaces: 390/405)

Central picture Legend: Cavopulmonary assist device: flow augmentation through the total cavopulmonary connection. (Characters including spaces: 90/90)

Glossary of Abbreviations

MCS, mechanical circulatory support

TCPC, total cavopulmonary connection

SVC, superior vena cava

IVC, inferior vena cava

RPA, right pulmonary artery

LPA, left pulmonary artery

VAD, ventricular assist device

Repair of single functional ventricle currently consists of staged surgical approach that terminates in a univentricular Fontan circulation. Since its introduction, Fontan palliation has dramatically improved the outcome for all forms of single ventricle heart disease [1,2]. However, Fontan survivors are committed for the remainder of their lives to a state of chronic circulatory inefficiency due to the lack of a subpulmonary ventricle.

This results in coexisting elevated systemic venous pressure and reduced cardiac output, known clinically as the Fontan paradox [3]. Combined, these problems have been clearly shown to progress to late Fontan failure and attrition [4]. Despite extensive clinical and research effort, therapies to prevent or reverse this circulatory decline remain extremely limited with no breakthroughs for decades [5]. With an increasing number of late Fontan survivors, Fontan failure is now a routinely encountered and challenging clinical problem.

We have theorized that replacement of the missing subpulmonary power source would reverse the Fontan paradox and shift the univentricular circulation toward more stable biventricular equivalency [6]. It would decongest the systemic venous and lymphatic circulations, while simultaneously improving cardiac output. If applied as durable long-term support, it could in theory preempt Fontan-associated disease progression by maintaining biventricular equivalency.

Despite the simplicity and attractiveness of this concept, the technologic considerations are complex and dissimilar to any other mechanical circulatory support (MCS) application. We have found that existing MCS technologies are ill-suited and unmodifiable to address Fontan circulatory inefficiency. Alternatively, we have focused on the development of an anatomically-specific device that can replace the missing subpulmonary power source and reverse the Fontan

paradox [7]. This report describes the computational and in vitro basis for an implantable cavopulmonary assist device concept that has potential to safely and durably restore biventricular equivalency in a univentricular circulation.

Methods:

Pump design: In previous studies, we have demonstrated that a remotely powered rotary pump, based on the von Karman viscous pump, can provide 4-way flow augmentation through the total cavopulmonary connection (TCPC) [7]. A biconical impeller suspended in the midst of the TCPC functions as a 2-sided centrifugal pump, drawing inflow from the superior and inferior vena cavae (SVC, IVC), and augmenting outflow to the left and right pulmonary arteries (LPA, RPA) at physiologic pressure. A modest pressure step-up of 6 mmHg has been shown in vitro and in vivo to restore the univentricular Fontan circulation to biventricular equivalency under normal physiologic conditions [6,7]. We have also demonstrated that a cavopulmonary assist device based on the von Karman viscous pump will not obstruct the systemic venous pathway in the event of rotational dysfunction, and will instead reduce kinetic energy loss in the TCPC [7].

Because an external power source would limit such a device to temporary use, a permanent power source was incorporated in the form of an outrunner brushless DC (BLDC) motor. In an outrunner motor, the rotating component is outside rather than inside (Figure 1). For an in-series pump situated in the Fontan venous pathway, this configuration is key to eliminating the risk of venous pathway obstruction because it allows preservation of a wide passage between the impeller and housing. As a result, the pump can serve in 2 distinctly different capacities:

rotating, it functions as a pump; non-rotating, it functions as a static flow diverter (Figure 2). Thus, it is intended to be beneficial even if it fails.

A biconical stator, containing iron laminations and copper windings, is located centrally within the impeller, and has no blood contact or moving parts. It is surrounded by a biconical rotor with embedded magnets as the only moving component. Rotor surface vanes provide low-pressure, high-volume augmentation of cavopulmonary flow (Video 1). A secondary (internal) flow path between the rotor and the stator is an inherent centrifugal pump and integrates several key functions: 1) electromagnetic flux transfer for motor torque; 2) heat dissipation; 3) bearing lubrication; 4) rotordynamic stabilization (Video 2). The housing is a double inlet, double outlet thin-walled hardcase shell that serves only to direct TCPC flow and structurally suspend the pump. Wiring from the stator travels through the central shaft to exit the housing via shaft struts. Because there is no external component bulk, the pump is no larger than the native TCPC, and is suitable for *in situ* implantation.

An advanced prototype was designed and fabricated at adult scale (25 mm dia inlets, 20 mm dia outlets) (Figure 3). Using computational fluid dynamic (CFD) modeling, impeller dimension and motor size were determined based on the torque required to achieve a pressure rise of 6-8 mmHg under physiologic conditions. Non-circumferential conical bearings support the rotor at each end. The impeller surface vane height is only 0.7 mm. The pump was tested initially in an open circuit, with no baseline imposed flow, using blood analog (water/glycerin 63/37, physiologic density 1060 kg/m^3, 3.2 cP). Testing was then performed in a static loop for pressure-flow (H-Q) performance, and lastly *in vitro* in a mock loop of a Fontan circulation for physiologic performance. For static performance, the pump was operated at 0-5600 RPM against 5 different resistances. Steady-state pressure head and flow rates were plotted to characterize

hydraulic (H-Q) performance. Inlet partial and complete occlusion performance was assessed. For physiologic performance testing, a Fontan mock circulatory system was utilized that includes compliance and resistance elements [7].

Results:

All design objectives were met, including: 1) pressure-flow performance of 0-14 mmHg pressure rise over 0-5600 RPM; 2) mean scalar shear stress < 100 Pa, transit time < 0.01s; 3) non-cavitating performance; 4) acceptable recirculation; 5) no pressure loss in the static condition (0 RPM). Heat dissipation was excellent, confirmed by reduction of core temperature at higher speed. Hydraulic performance was consistent over a wide range of cardiac output (Figure 4). A peak pressure of 14 mmHg was achieved at the highest speed. The pump generated 5 L/min of flow and 6 mmHg pressure head at 4000 RPM, and 5 L/min of flow and 8 mmHg pressure head at 5600 RPM. The in-vitro pump performance was consistent with the design specifications and CFD modeling (6-8 mmHg pressure rise under physiologic conditions). The pump generated inflow from both the SVC and IVC equally to both pulmonary arteries for SVC:IVC inflow ratios ranging from 30:70 to 50:50. The pump effectively mixed inflow from both inlets with symmetric outflow distribution (hepatic factor, Video 1). The power draw was less than 6W at maximal speed, and is expected to improve with further optimization. Because the surface vane profile is so low, there is flexibility to increase vane height for higher pressure performance without compromising the no-obstruction constraint.

In *in vitro* physiologic mock loop testing, the device effectively reversed the Fontan (Figure 5). With increasing RPM, ventricular end-diastolic pressure and aortic pressure

increased. At 5000 RPM, the pump converted a cavopulmonary pressure head of positive 2.8 mmHg to negative 4.8 mmHg, replacing a small energy loss with a proportionally larger gain. It boosted pulmonary arterial pressure by 6 mmHg, and increased preload sufficient to increase cardiac output by 12.8%. Vena caval pressure was reduced 1.4 mmHg, which is significant in this segment of the circulation where even small reduction of pressure is beneficial to splanchnic health. Increase in pump speed beyond 5000 RPM caused a larger negative cavopulmonary pressure head but did not lead to a measurable increase cardiac output. When the pump was stopped (0 RPM), there was no discernible pressure drop, validating the no-obstruction design constraint. Importantly, in the stopped condition, TCPC turbulence was reduced compared to the condition with no pump installed.

Discussion:

Amongst the many significant advances in the treatment of congenital heart disease over the past 5 decades, single ventricle palliation has had perhaps the largest impact. Nonetheless, it was predicted by its' innovators that it may be incompatible with a normal lifespan and require improvement or modification [9-11]. As predicted, Fontan-associated disease now represents one of the most significant challenges in the field. Although Fontan palliation is lifesaving, it carries a lifelong chronic disease burden that has no primary preventive therapy and is ultimately life-limiting [12,13]. As a reflection of its palliative nature, late Fontan attrition is relatively constant suggesting that immutable factors play a role, and 30-year survival is only 43-70% [14-16].

Solutions to address Fontan-associated disease have been largely incremental and of unclear benefit, and we may have reached a plateau. Fontan optimization can at best only

prolong an inherently inefficient system because it does not address the underlying physiologic deficit: the lack of a subpulmonary ventricle. To date, little effort has focused on mechanical replacement of a subpulmonary power source, presumably because a comprehensive solution is unobvious and highly complex. However, replacement of the missing subpulmonary power source is physiologically compelling: it will normalize systemic venous pressure, decongest the lymphatic circulation, and normalize ventricular loading conditions, emulating biventricular efficiency. Given the ongoing problems with Fontan-associated disease, it is reasonable to reconsider the current paradigm. Rather than Fontan perpetuation, a preferable strategy may be to reverse the Fontan [17].

Fontan failure is largely non-ventricular failure: Although those with failing Fontan circulations may exhibit classic features of congestive heart failure, the primary cause is not typically ventricular systolic dysfunction. Prior to end-stage Fontan disease, ejection fraction is preserved in >70% of patients; diastolic dysfunction predominates [18]. While the mechanisms are complex and multi-factorial, Fontan diastolic dysfunction has been largely attributed to chronic preload deprivation [19,20]. Over time, abnormal loading conditions (decreased preload, increased afterload) result in cardiomyopathic remodeling and fibrosis [21], and eventual systolic dysfunction. Thus, it can be said that the Fontan circulation predisposes the single ventricle to fail. Furthermore, efforts that target improvement in ventricular function as a solution to Fontan disease may be misguided; it may be of greater benefit to provide cavopulmonary assistance.

Cavopulmonary assist specifically addresses the lack of a subpulmonary power source, and will in turn normalize ventricular loading conditions and improve function. In the setting of

diastolic dysfunction but preserved systolic function, a modest increase in preload (~1-3 mmHg) will improve myocardial performance and cardiac output (opposite primary myocardial failure).

Transplantation is, in a sense, a definitive therapy for Fontan failure in that it reinstates a subpulmonary ventricle, but it does so at the cost of a different disease process. There aren't sufficient donor organs available to transplant all single ventricle patients. Due to listing criteria, most Fontan patients won't receive a donor organ until they have end-stage disease with advanced co-morbidities. Transplant survival of <50% at 10 years is arguably no better than the natural history of late Fontan attrition [22]. For these reasons, transplantation is not a comprehensive solution and represents end-stage therapy.

Fontan optimization falls short: Strategies to optimize Fontan hemodynamics have logically targeted the TCPC, where anatomic factors may result in significant power loss [23-25]. These have included various vena caval offset configurations, as well as a Fontan 'Y' conduit to reduce power loss in the inferior vena caval distribution [26]. Although these modifications have been applied clinically, they have not had significant impact. The maximal pressure gain that can be derived from passive flow optimization (~1-2 mmHg) does not fully correct the circulatory deficit and, as a result, does not meaningfully improve circulatory status. By comparison, consider normal biventricular physiology in which the right ventricle provides a cavopulmonary pressure step-up of ~6-8 mmHg. To make a clinically meaningful improvement in Fontan, it is necessary to add pressure energy at the TCPC by a similar amount.

Limitations of current MCS technology applied to Fontan: The application of existing MCS devices for Fontan failure is limited, highly variable, and associated with poor outcomes [27-30]. It has generally focused on the application of systemic support in end-stage Fontan disease due to the nature of existing technologies. Nearly all MCS technologies are intended for systemic support. However, depending on the circumstances, the device is likely mismatched to Fontan circulatory needs, i.e. left-sided support to address a right-sided deficit. Anecdotally, existing MCS appears to be better suited for ventricular "pump" failure in Fontan, rather than for Fontan failure secondary to lack of a subpulmonary ventricle. In the setting of preserved systolic function, systemic MCS in Fontan is redundant; it may needlessly congest the right-sided circulation where the circulatory bottleneck exists and exacerbate Fontan disease.

Existing MCS applied strategically to the right side of the Fontan circulation has been reported [31]; however, it is logistically impractical for several reasons: 1) the Fontan must be taken down to accommodate a single inflow, single outflow device; 2) a systemic MCS device is not optimized to the very low pressure rise desired for cavopulmonary assist, increasing risk for device failure; 3) the right-sided circulation is dependent on the device, making device dysfunction lethal; 4) device operational lifespan is limited, and therefore not a long-term solution. Given these considerations, the use of existing MCS technology in Fontan is limited to end-stage disease as bridge therapy, if it is used at all.

Technical considerations for long-term Fontan reversal: Dedicated right-sided circulatory support of the Fontan circulation presents a number of caveats that are uniquely challenging (Table 1). Technically, a cavopulmonary assist device is not a ventricular assist device (VAD)

because it provides support where no ventricle exists. It is intended to function as a low-input auxiliary right-sided pump to maintain low systemic venous pressure and preload to the systemic ventricle, identical to the essential function of the right ventricle in a biventricular circulation [32].

Although comparatively a weak pump, the inherent performance a von Karman viscous pump is ideal for the Fontan circulation. As a dynamic pump, it can provide consistent pressure rise over a wide range of cardiac output, making it responsive to physiologic demand. Low hydraulic efficiency also makes it less likely to generate suction, vein collapse, and cavitation, and tolerant to physiologic variation in systemic venous return. Similarly, it is unlikely to generate excessive downstream pressure, reducing risk for lung perfusion injury. The majority of existing MCS devices are displacement pumps that must vary RPM to vary flow rate, making them susceptible to suction, and unresponsive to physiologic demand thereby limiting exercise capacity.

The TCPC is the best-known geometry for passive cavopulmonary flow [23]. Thus, our strategy has been to retain the TCPC as a default flow path, and design an anatomically-specific pump to add pressure energy within it. A central diverting body at the TCPC intersection will split incoming flow toward each outlet, significantly reducing turbulent energy loss [33,34]. By rotating a central stabilizing body, suspended within the TCPC independent of the vessel walls, fluid pressure and velocity is increased, transforming it from a static flow diverter to a pump. We also anticipate that a permanently implanted device will eventually fail. In Fontan, a pump situated in the center of the flow path cannot impede flow (Figure 6). This is a critical safety consideration in young Fontan patients with decades of life expectancy ahead of them.

The ideal pressure rise for a cavopulmonary assist device is not yet clinically determined. We have shown in this study, and in other *in vitro* mock circulatory studies of a Fontan circulation that 6 mmHg pressure step-up will restore biventricular equivalency under normal physiologic conditions [7,8]. This pressure rise correlates with normal circulatory physiology. The presence of increased pulmonary vascular resistance in Fontan may impact the magnitude of pressure rise required. Extremely elevated pulmonary resistance is incompatible with late Fontan survival; therefore, we believe the need for a pressure increase significantly greater than ~15 mmHg is unlikely. Further, in the cavopulmonary circulation, the margin to apply an aggressive pressure step-up is limited by baseline systemic venous pressure. For example, the application of a 20 mmHg pressure step-up in the TCPC in which baseline systemic venous pressure is 16 mmHg will induce negative (-4 mmHg) systemic venous pressure, leading to suction collapse and flow disruption.

In general, MCS devices are not placed in line or in series with the circulation, but are rather placed in parallel (i.e. paracardiac) due to risk of device obstruction of the native flow path. This concern is amplified for a Fontan pump situated in the lowest pressure segment of the circulation, where seemingly trivial obstruction can induce hemodynamic instability. An implantable Fontan pump must have no potential for mechanical obstruction in the event of dysfunction.

Emerging technologies: Single functional ventricle is a final frontier for MCS therapy, and concepts for dedicated Fontan circulatory support are currently evolving [8,35]. To date, nearly all have focused on modification of existing technology (unidirectional axial or centrifugal VADs) to operate in the low-pressure Fontan environment. Although these may suffice as bridge

therapy, they lack the technologic rigor required for safe and durable long-term support. They are incapable of supporting flow in all 4 limbs of the cavopulmonary connection, and will induce back-pressure elevation in the opposing systemic venous territory. They are capable of mechanical obstruction, a prohibitive issue when the right-sided circulation is dependent on the device. Due to motor configuration, they may be bulky and not fit within the confines of the TCPC. Lastly, if the Fontan pathway is modified to accommodate a unidirectional flow device, the resulting pathway will not support passive cavopulmonary flow in the event of device dysfunction. With respect to safety and durability, a Fontan pump that offers multi-directional flow, *in situ* anatomic placement, and a contingency plan for failure is preferable.

Clinical implications: Cavopulmonary assist reframes single ventricle palliation from a problem with no solution to a problem with an obvious solution. The challenge lies in creating a technology that can safely and durably implement it. If successfully translated, it would represent a first-ever targeted therapy for Fontan failure. It would also permit biventricular equivalency to be maintained in a univentricular circulation prior to clinical failure, preempting Fontan disease. For Fontan patients who have few options to alter their inevitable disease progression, this concept has exciting potential to shift the paradigm for single ventricle therapy from palliation to cure.

The clinical vision for a Fontan-specific cavopulmonary assist device is much different from current MCS strategy. Rather than reserving MCS for end-stage salvage, it may be better to apply it preemptively for biventricular health maintenance. Thus, the device may not necessarily be limited to advanced Fontan failure, and may be considered earlier. For Fontan patients, the implications are starkly different: a lifetime of chronic disease progression with systemic MCS

as end-stage therapy versus cavopulmonary assist to enable long-term biventricular health and wellness, potentially for decades.

Limitations: This report presents early stage electromechanical feasibility for an implantable cavopulmonary assist device concept. Such a therapy has never been implemented clinically; therefore, discussion of clinical application and duration of support is theoretical. Substantial technologic development remains to be performed, and significant obstacles may arise in future design iteration. Thrombogenicity performance remains to be determined, and device durability is unknown. The power source has not yet been determined, although it is envisioned to be powered wirelessly. Until a device is fully developed, regulatory approved, and enters clinical trial, the translational impact of long-term Fontan reversal will remain speculative.

Conclusions: After Fontan repair of single functional ventricle, patients are trapped for the remainder of their lives in a cycle of chronic circulatory inefficiency. Despite dramatic improvement in surgical technique, perioperative care, and long-term surveillance, late Fontan failure and attrition remains an intractable problem for which there is no primary or preventive therapy. An early stage implantable cavopulmonary assist device shows promising potential to reverse the Fontan paradox and preempt Fontan-associated disease as a curative therapy. It represents a significant opportunity to fundamentally shift the paradigm for single ventricle care to one based on biventricular health.

Table 1. Desirable technical features for a long-term cavopulmonary assist device:

1. Simplicity. A single pump, with one moving part, that serves as a low-input primer for the systemic ventricle.
2. Multi-directional flow. Flow augmentation in all 4 distributions of the TCPC (SVC/IVC inflow, RPA/LPA outflow).
3. Low pressure performance. Low pressure (~6-8 mmHg), high volume flow augmentation, similar to normal right ventricular hemodynamics.
4. Wide performance range. Consistent pressure rise over a wide range of cardiac output and variable physiologic demand, independent of pump speed.
5. Unobstructive. An in-line pump in the Fontan venous pathway must account for pump failure, with minimal or no obstruction risk as a failure default.
6. TCPC as the preferred default flowpath. The failed (0 RPM) condition should ideally optimize passive TCPC flow as an unsupported Fontan circulation.
7. Permissive preload and afterload performance. Low hydraulic efficiency to reduce risk of excessive negative upstream pressure (suction, vein collapse, cavitation), and excessive positive downstream pressure (perfusion lung injury). It will also permit tolerance to the natural inflow instabilities that occur in systemic venous return (supine vs upright posture, cough, Valsalva).
8. Mixing. Symmetric hepatic factor distribution to prevent pulmonary arteriovenous malformation (Video 1).

9. No barrier to recirculation. To reduce thrombogenicity and obstruction risk.
10. Small size. *In situ* implantation to avoid physical encroachment on adjacent structures (e.g. aorta, common atrium, pulmonary veins).

References:

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240-8.
2. Kreutzer G, Galindez E, Bono H, DePalma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 1973;66:613-21.
3. de Leval MR. The Fontan circulation: What have we learned? What to expect? Pediatr Cardiol 1998;19:316-20. Review.
4. Rychik J. The relentless effects of the Fontan paradox. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2016;19:37-43.
5. Gewillig M, Brown SC. The Fontan Circulation after 45 years: Update in Physiology. Heart 2016;102;1081-6.
6. Rodefeld MD, Boyd JH, Myers CD, Lalone BJ, Bezruczko A, Potter AW, et al. Cavopulmonary assist: circulatory support for the univentricular Fontan circulation. Ann Thorac Surg 2003;76:1911-6.
7. Rodefeld MD, Coats B, Fisher T, Giridharan GA, Chen J, Brown JW, et al. Cavopulmonary assist for the univentricular Fontan circulation: von Karman viscous impeller pump. J Thorac Cardiovasc Surg 2010;140:529-36.
8. Rodefeld MD, Frankel SH, Giridharan GA. Cavopulmonary assist: (Em)powering the univentricular Fontan circulation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2011;14:45-54.

9. Fontan F, Kirklin JW, Fernandez G, Costa F, Naftel DC, Tritto F, et al. Outcome after a "perfect" Fontan operation. Circulation 1990;81:1520-36.
10. Kreutzer C, Kreutzer J, Kreutzer GO. Reflections on 5 decades of the Fontan Kreutzer procedure. Front Pediatr 2013;1:45-60.
11. de Leval MR. The Fontan circulation: a challenge to William Harvey? Nat Clin Pract Cardiovasc Med 2005;2:202-8.
12. Rychik J. Forty years after the Fontan: a failed strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2010;13:96-100.
13. Veldtman GR, Opotowsky AR, Wittekind SG, Rychik J, Penny DJ, Fogel M, et al. Cardiovascular adaptation to the Fontan circulation. Congenit Heart Dis 2017;12:699-710.
14. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation 2015;132:2118-25.
15. Pundi KN, Johnson JN, Dearani JA, Li Z, Hinck CA, Dahl SH, Cannon BC, O'Leary PW, Driscoll DJ, Cetta F. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 Patients. J Am Coll Cardiol. 2015;66:1700-10.
16. Australia and New Zealand Fontan Registry: Report 2016. 2016:1-10.
17. Rodefeld MD. The Fontan circulation: time for a moonshot? J Thorac Cardiovasc Surg 2018;156:252-3.
18. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. J Am Coll Cardiol 2008;52:85-98.

19. Averin K, Hirsch R, Seckeler MD, Whiteside W, Beekman RH, Goldstein BH. Diagnosis of occult diastolic dysfunction late after the Fontan procedure using a rapid volume expansion technique. Heart 2016;102:1109-14.

20. De Mey W, Cools B, Heying R, Budts W, Louw JJ, Boshoff DE, et al. Can a volume challenge pinpoint the limiting factor in a Fontan circulation? Acta Cardiol 2015;70:536-42.

21. Rathod RH, Prakash A, Powell AJ, Geva T. Myocardial fibrosis identified by cardiac magnetic resonance late gadolinium enhancement is associated with adverse ventricular mechanics and ventricular tachycardia late after Fontan operation. J Am Coll Cardiol 2010;55:1721-8.

22. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, et al. American Heart Association Adults With Congenital Heart Disease Committee of the Council on Clinical Cardiology and Council on Cardiovascular Disease in the Young, and the Council on Functional Genomics and Translational Biology. Transplantation and Mechanical Circulatory Support in Congenital Heart Disease: A Scientific Statement From the American Heart Association. Circulation 2016;133:802-20.

23. Bove EL, de Leval MR, Migliavacca F, Balossino R, Dubini G. Toward optimal hemodynamics: computer modeling of the Fontan circuit. Pediatr Cardiol 2007;28:477-81.

24. Sundareswaran KS, Pekkan K, Dasi LP, Whitehead K, Sharma S, Kanter KR, et al. The total cavopulmonary connection resistance: a significant impact on single ventricle hemodynamics at rest and exercise. Am J Physiol Heart Circ Physiol 2008;295:H2427-35.

436 25. Tang E, Restrepo M, Haggerty CM, Mirabella L, Bethel J, Whitehead KK, et al.
437 Geometric characterization of patient-specific total cavopulmonary connections and its
438 relationship to hemodynamics. JACC Cardiovasc Imaging 2014;7:215-24.
439 26. Marsden AL, Bernstein AJ, Reddy VM, Shadden SC, Spilker RL, Chan FP, et al.
440 Evaluation of a novel Y-shaped extracardiac Fontan baffle using computational fluid
441 dynamics. J Thorac Cardiovasc Surg 2009;137:394-403.
442 27. Arnaoutakis GJ, Blitzer D, Fuller S, Eckhauser AW, Montenegro LM, Rossano JW, et al.
443 Mechanical Circulatory Support as Bridge to Transplantation for the Failing Single
444 Ventricle. Ann Thorac Surg 2017;103:193-7.
445 28. Horne D, Conway J, Rebeyka IM, Buchholz H. Mechanical circulatory support in
446 univentricular hearts: current management. Semin Thorac Cardiovasc Surg Pediatr Card
447 Surg Annu 2015;18:17-24.
448 29. Adachi I, Burki S, Fraser CD. Current Status of Pediatric Ventricular Assist Device
449 Support. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2017;20:2-8.
450 30. Woods RK, Ghanayem NS, Mitchell ME, Kindel S, Niebler RA. Mechanical circulatory
451 support of the Fontan patient. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu
452 2017;20:20-27.
453 31. Prêtre R, Häussler A, Bettex D Genoni M. Right-sided univentricular cardiac assistance
454 in a failing Fontan circulation. Ann Thorac Surg 2008;86:1018-20.
455 32. Furey SA, Zieske HA, Levy MN. The essential function of the right ventricle. Am Heart
456 J 1984;107:404-10.

33. Soerensen DD, Pekkan K, de Zelicourt D, Sharma S, Kanter K, Fogel M, et al. Introduction of a new optimized total cavopulmonary connection. Ann Thorac Surg 2007;83:2182-90.

34. Desai K, Haggerty CM, Kanter KR, Rossignac J, Spray TL, Fogel MA, et al. Haemodynamic comparison of a novel flow-divider Optiflo geometry and a traditional cavopulmonary connection. Interact Cardiovasc Thorac Surg 2013;17:1-7.

35. Broda CR, Taylor DA, Adachi I. Progress in experimental and clinical subpulmonary assistance for Fontan circulation. J Thorac Cardiovasc Surg 2018;156:1949-56.

Figure Legend:

Figure 1: Outrunner brushless DC motor: A. Traditional motor design with inner rotating component. B. Outrunner motor design with outer rotating component and stationary central component.

Figure 2: Implantable cavopulmonary assist device concept. A central impeller contains the motor (impeller support shaft and struts not shown). The external housing is a hard case, thin-walled shell that has no component bulk and serves only to direct Fontan flow. The wide gap between the impeller and the housing must support passive TCPC flow in the event of device dysfunction.

Figure 3: Advanced prototype, adult scale. A: Design schematic showing housing with mounted impeller. Wiring travels from the stator via the central shaft and strut to exit the housing. The only moving component is the rotor. A secondary flow path allows for inflow at each axial end, with outflow at the equatorial gap (Video 2). B: Design schematic showing patulous channel to prevent obstruction in the event of rotational failure. Rotor surface shows 0.7 mm height curved surface vanes. C: Assembled prototype as tested and demonstrated in video.

Figure 4: Hydraulic performance. H-Q curve demonstrates pressure and flow performance.

Figure 5: In vitro mock loop parameter showing reversal of the failing Fontan circulation with cavopulmonary assist. Fontan baseline includes pump in TCPC in stalled condition.

VIP, viscous impeller pump; HR, heart rate; SV, stroke volume; CO, cardiac output; CO% increase, percent increase from baseline Fontan cardiac output; VCP, vena caval pressure; PAP, pulmonary artery pressure; CPPH, cavopulmonary pressure head (pump ΔP) = vena caval pressure – pulmonary artery pressure; AoP, aortic pressure.

Figure 6: Pump implantation (conceptual). The cavopulmonary assist device is implanted in situ in the TCPC and serves to modestly augment cavopulmonary flow. The device is compatible with either lateral tunnel and extracardiac conduit Fontan construction. Graft extensions allow for suturing, with a total of 4 anastomoses. Grafts can be extended or tailored to address anatomic issues. Two pumps are depicted. The systemic ventricle performs the majority work load. It is served by a low-input cavopulmonary assist device to normalize preload to the systemic ventricle, in addition to reducing systemic venous pressure. (TCPC: total cavopulmonary connection; SVC: superior vena cava; IVC: inferior vena cava; PA: pulmonary artery)

Video legend:

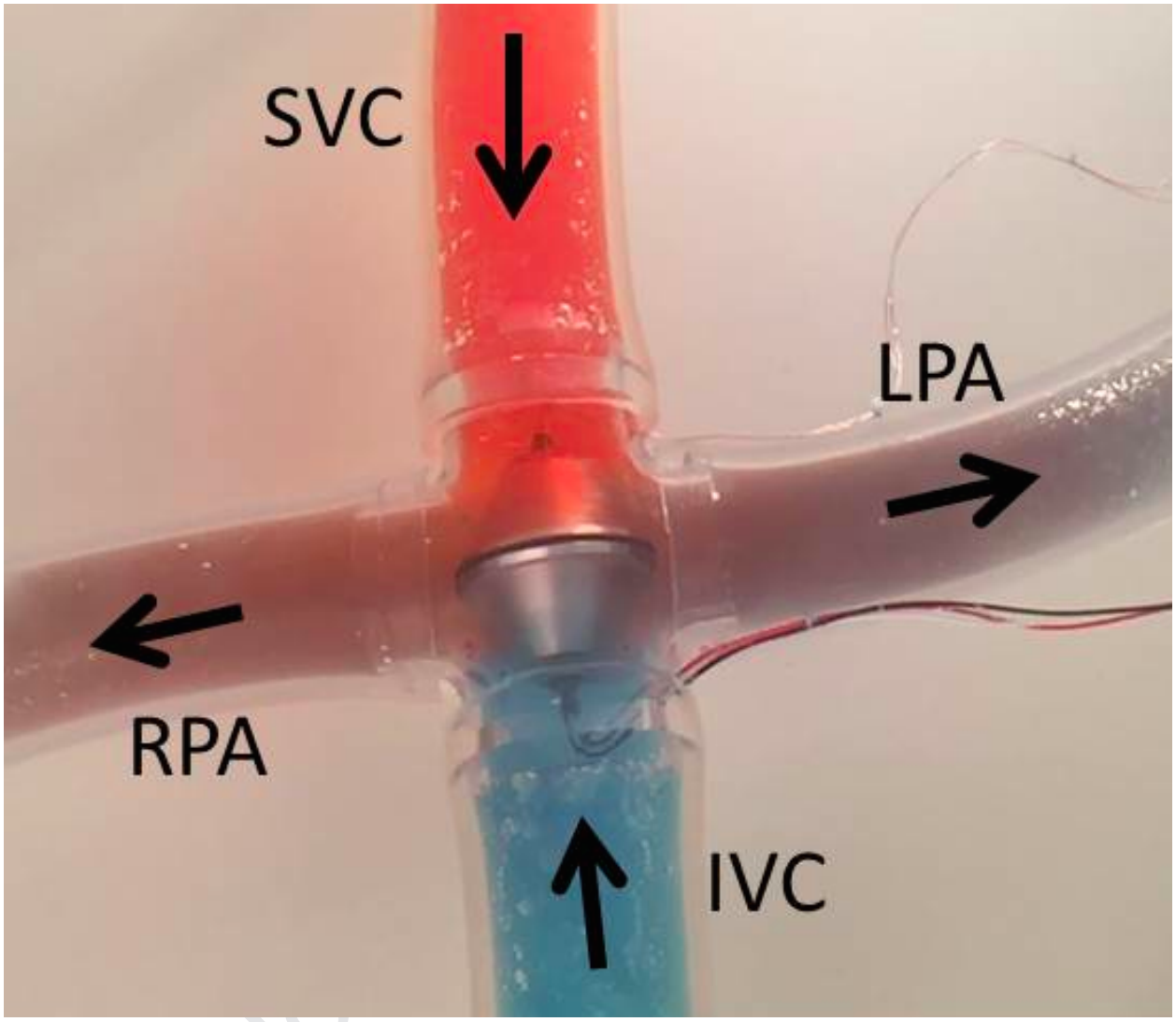
Video 1: Primary (external) flow path. Open static circuit; flow is induced by the pump. Yellow and blue contrast represent systemic venous inflow. The green outflow represents left and right pulmonary arterial flow. Mixing indicates symmetric hepatic factor distribution.

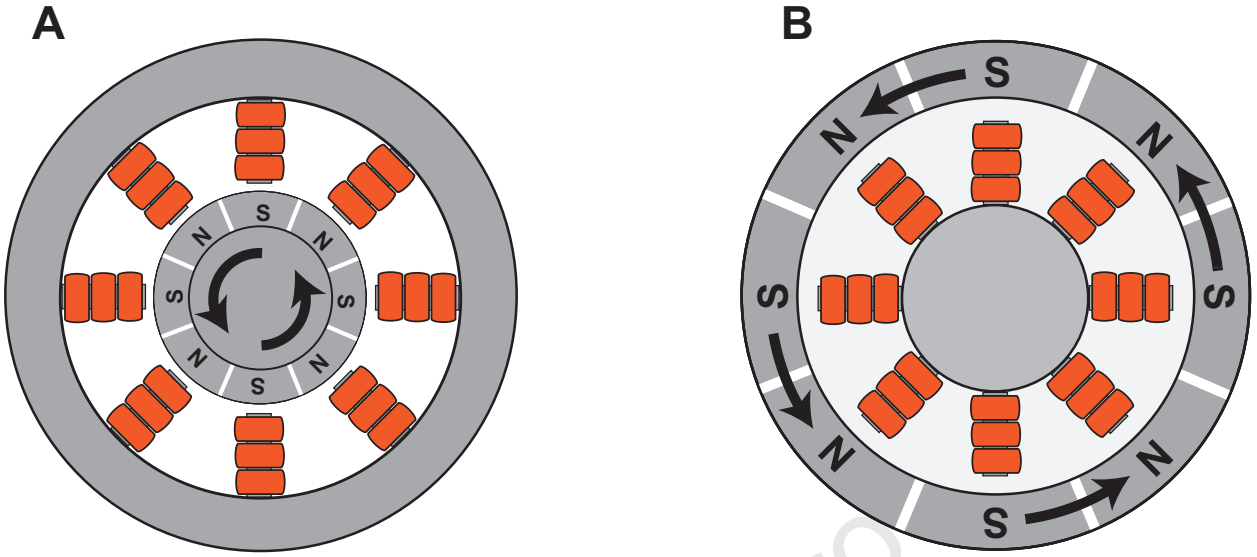
Video 2: Secondary (internal) flow path. Open static circuit; flow is induced by the pump. Contrast injection flows selectively through the internal flow path, with dispersion of outflow at

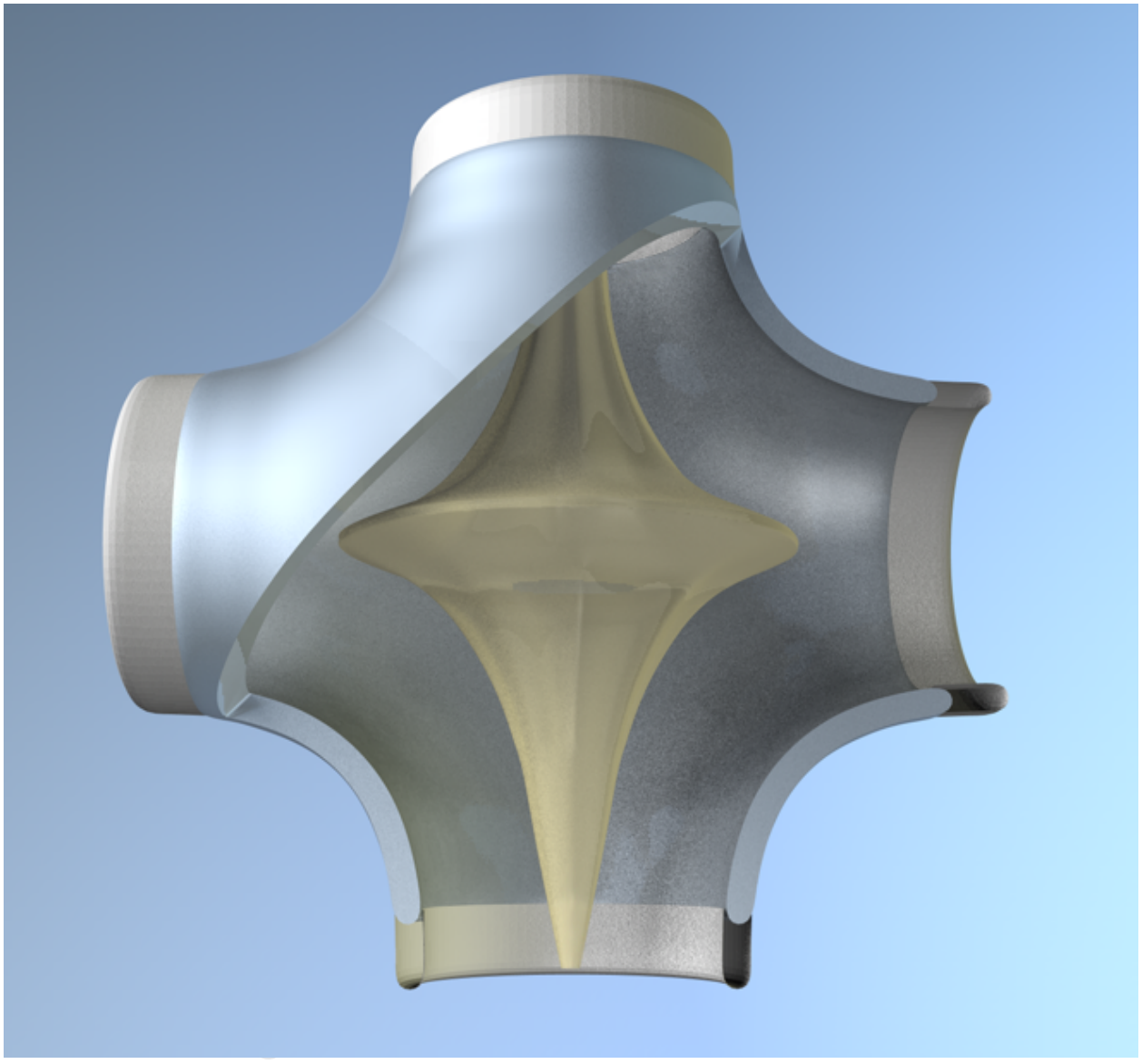
522 the equatorial midline. Internal path flow is essential to pump function for heat dissipation,

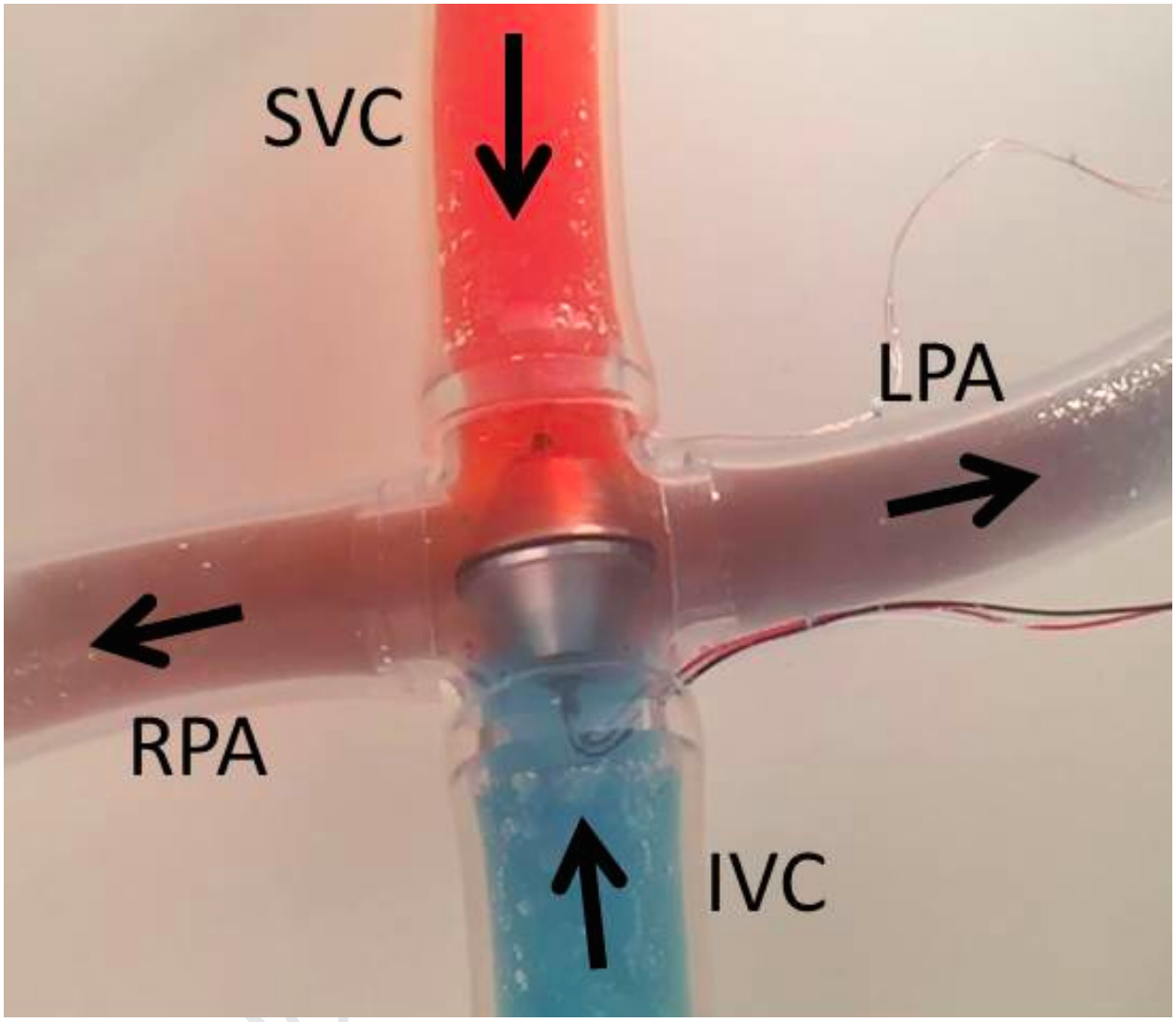
523 bearing flushing, and to reduce risk of recirculation, stasis, and thrombosis.

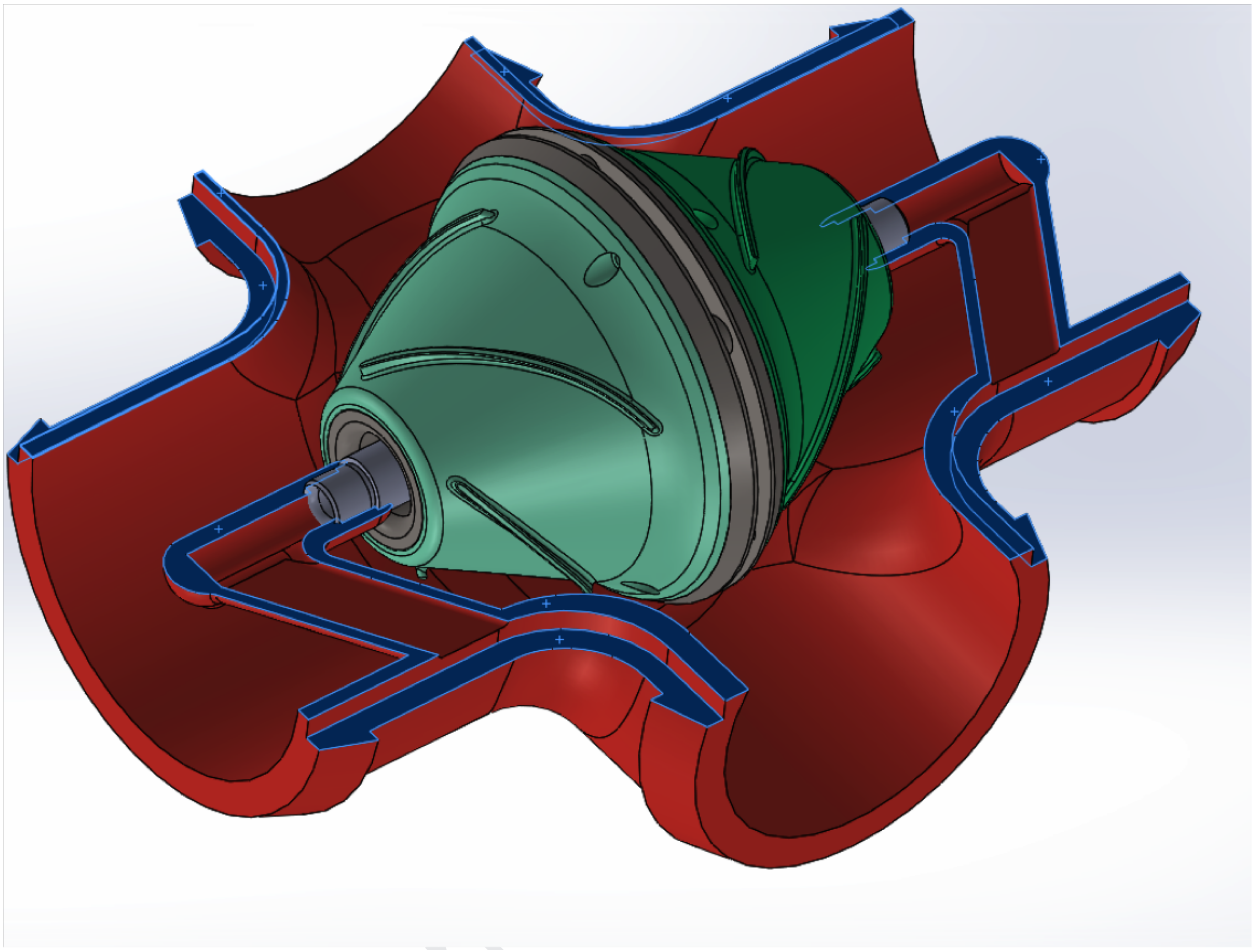
Case	VIP Speed (RPM)	HR (beats/min)	CO (L/min)	CO % increase	VCP (mmHg)	PAP (mmHg)	CPPH (mmHg)	AoP (mmHg)
Fontan Baseline	0	75	3.9	-	17.5	14.7	2.8	98.3/57.4
Fontan + VIP	3000	75	4.1	5.1%	17	16.6	0.4	102.3/60.5
Fontan + VIP	4000	75	4.3	10.3%	16.8	18	-1.2	111.9/66.7
Fontan + VIP	5000	75	4.4	12.8%	16.1	20.8	-4.8	113.6/69.0

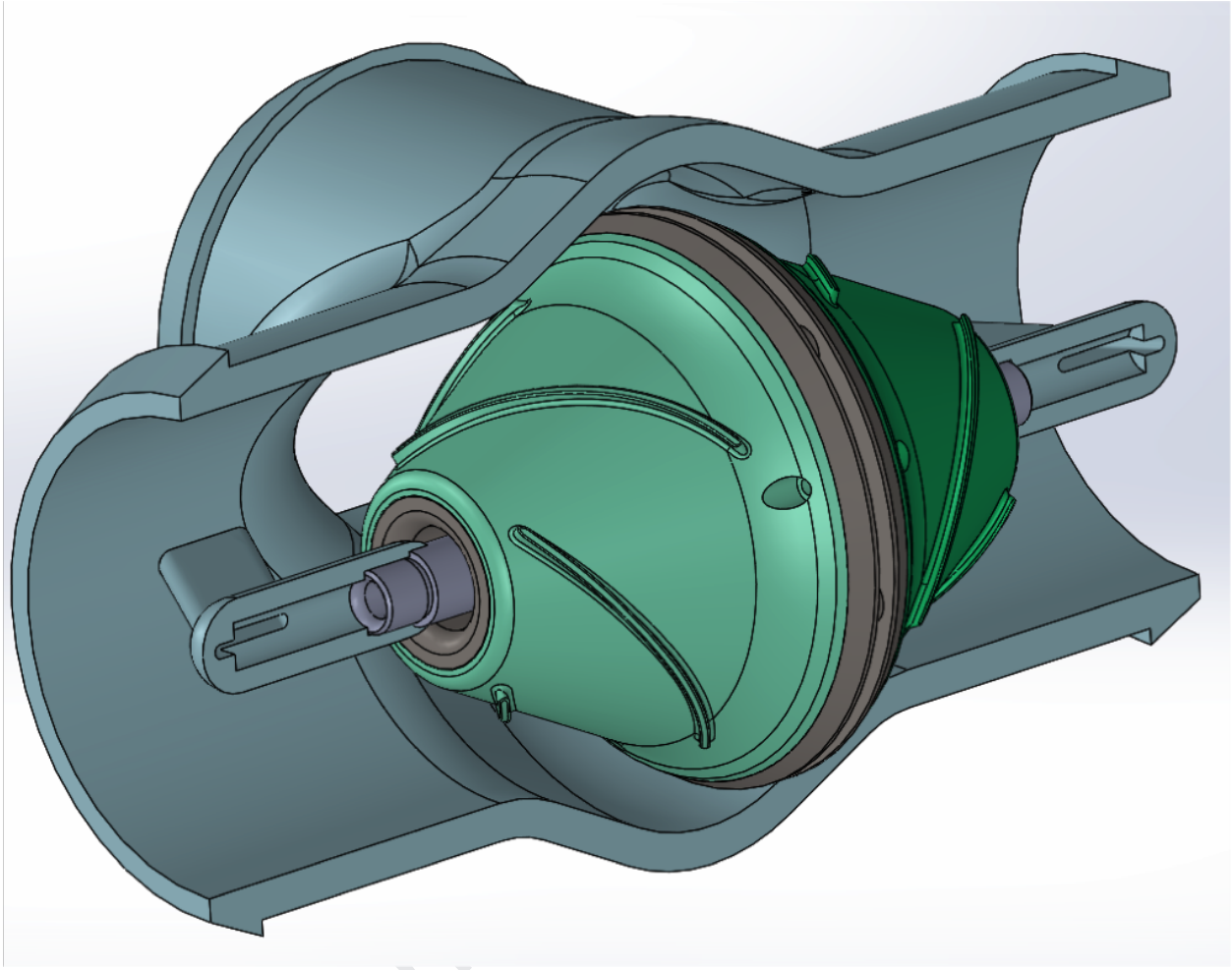

SVC
LPA
RPA
IVC

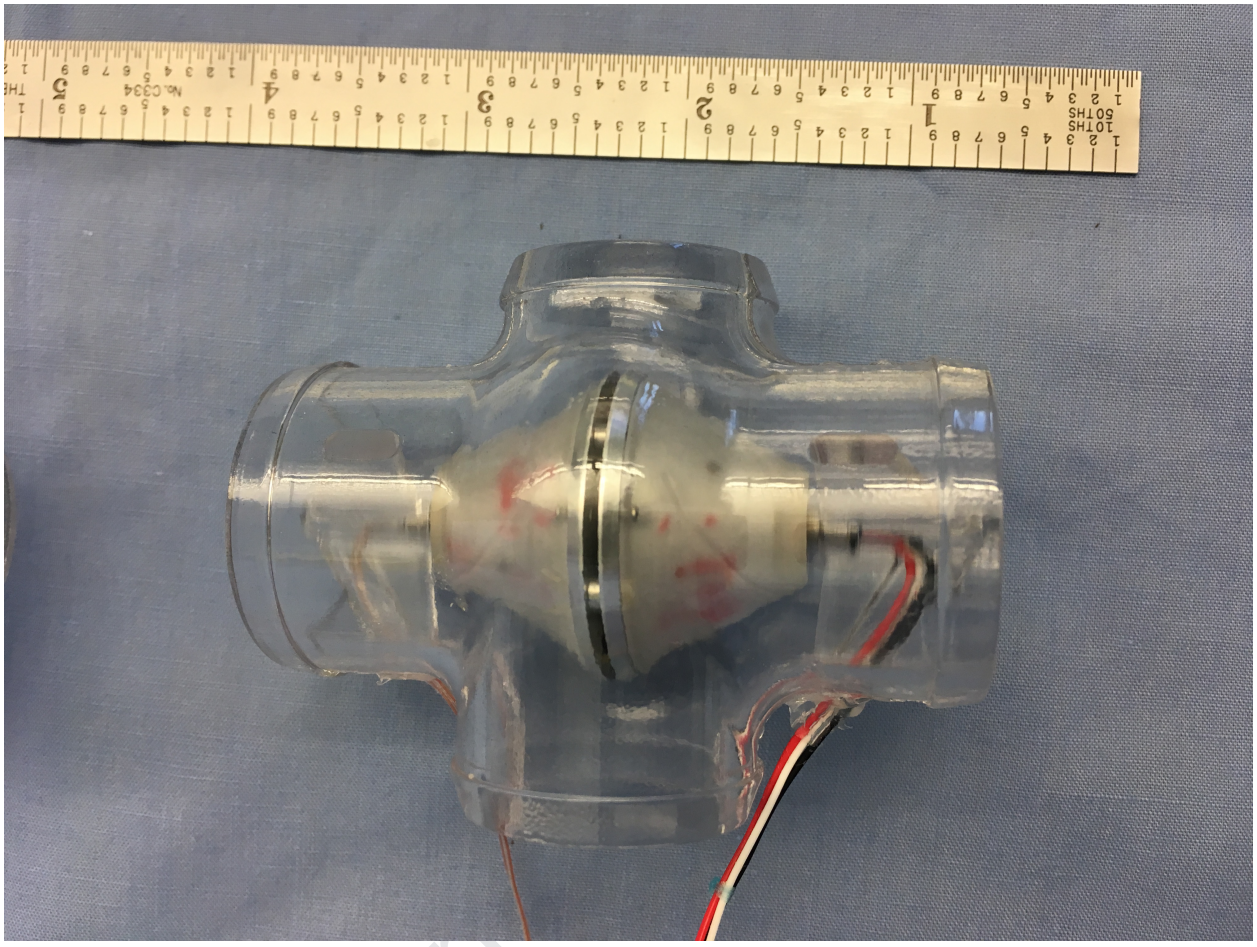


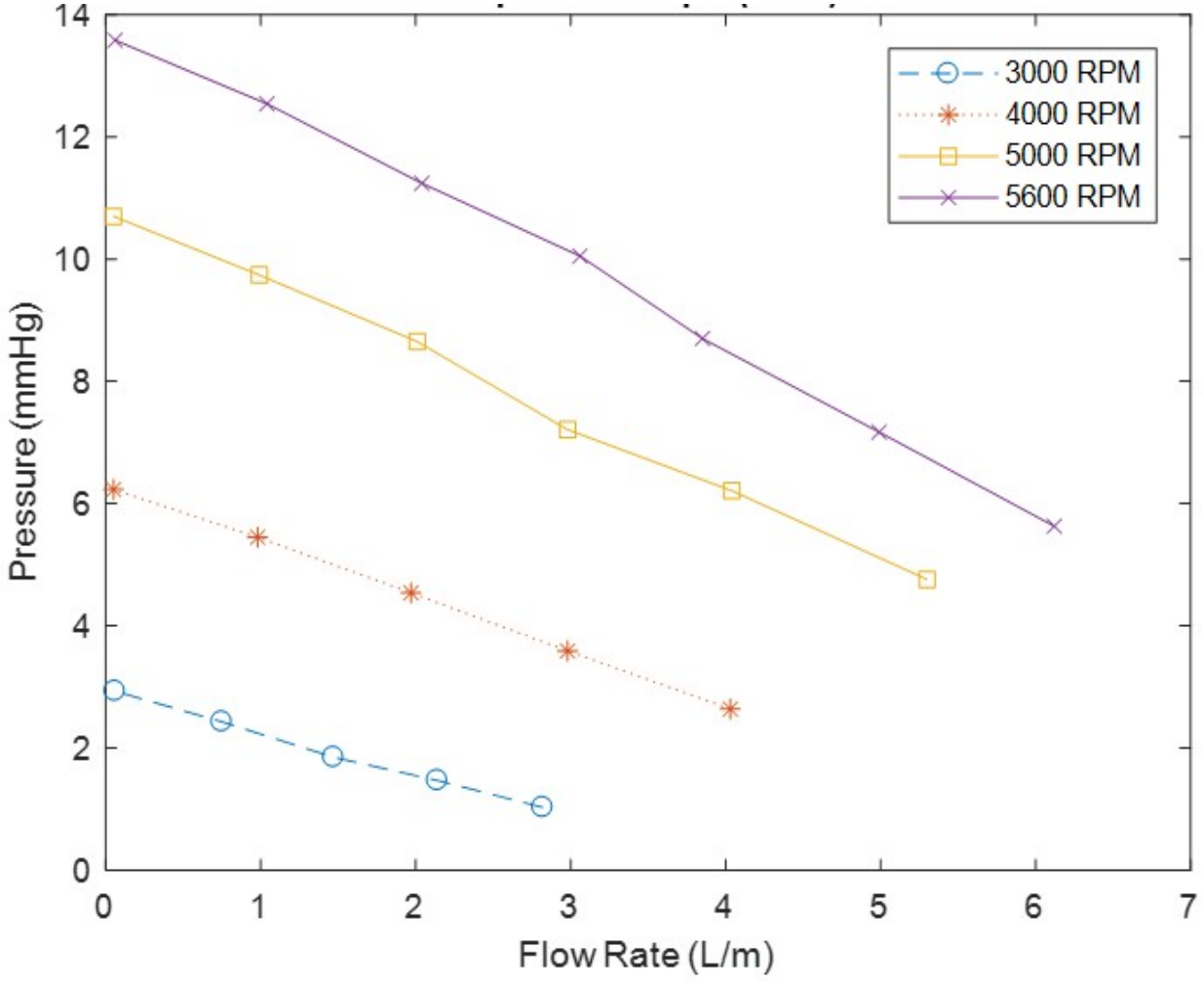


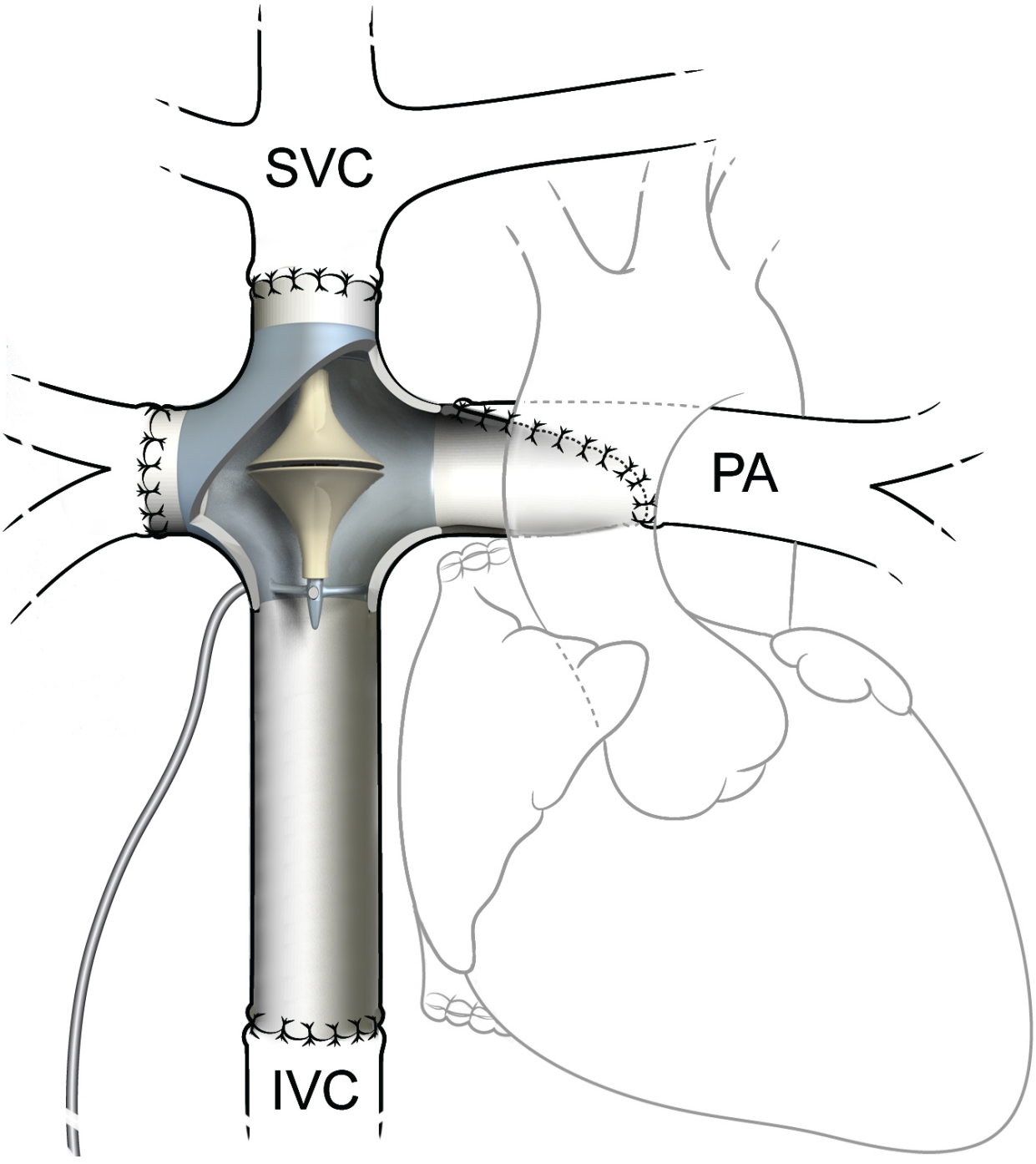

SVC
LPA
RPA
IVC

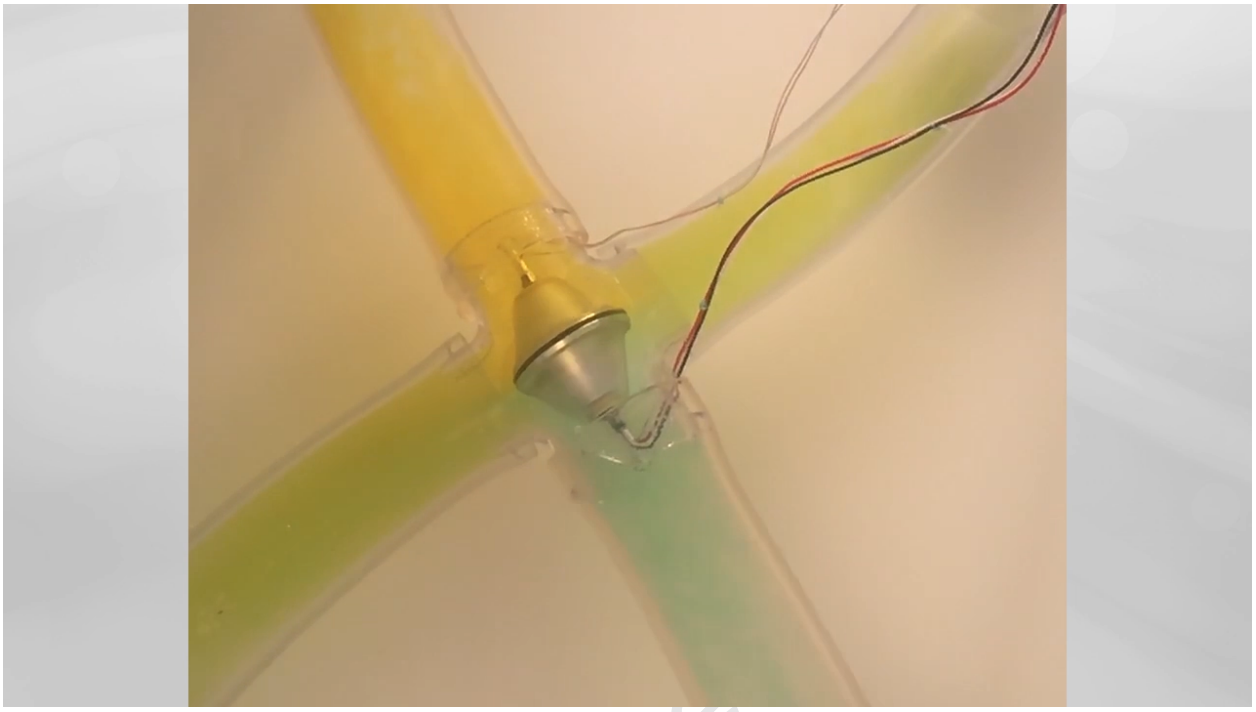


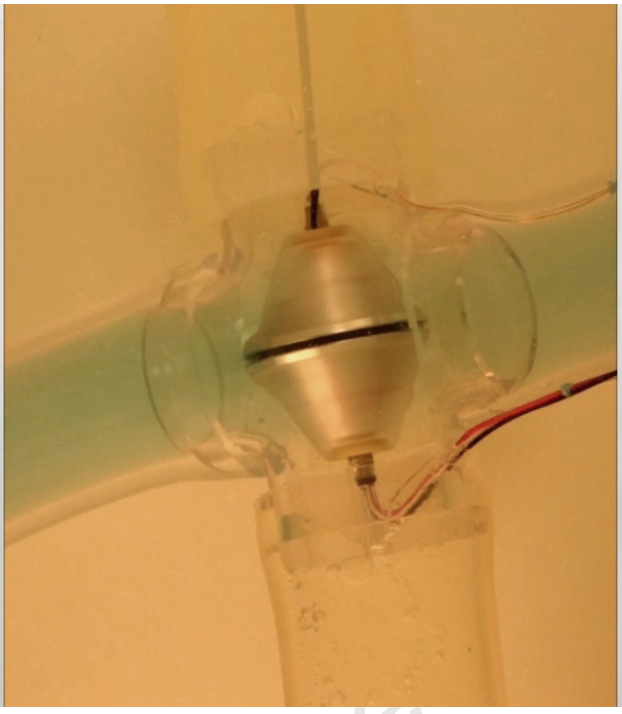





3000 RPM
4000 RPM
5000 RPM
5600 RPM
Pressure (mmHg)
Flow Rate (L/m)
0
2
4
6
8
10
12
14
0
1
2
3
4
5
6
7


SVC
PA
IVC





Cavopulmonary assist device for long-term Fontan reversal

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