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Ex Vivo Assessment of a Parabolic-Tip Inflow Cannula for Pediatric Continuous-Flow VADs

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Abstract

To address the challenge of unloading the left ventricle during pediatric mechanical circulatory support using next-generation rotary blood pumps, a novel inflow cannula was developed. This unique inflow cannula for pediatric, continuous-flow, left ventricular assist devices (VADs) with a parabolic-shaped inlet entrance was evaluated alongside a bevel-tip and fenestrated-tip cannula via an *ex vivo*, isolated-heart experimental setup. Performance was characterized using two clinical scenarios of over-pumping and hypovolemia, created by varying pump speed and filling preload pressure respectively, at ideal and off-axis cannula placement to assess ventricular unloading and positional sensitivity. Quantitative and qualitative assessments were performed on the resultant hemodynamics and intra-ventricular boroscopic images to classify conditions of non-suction, partial, gradual or severe entrainment, and ventricular collapse. The parabolic-tip cannula was found to be significantly less sensitive to placement position (p-values < 0.001) than the bevel-tip cannula under all conditions, while not statistically different from the fenestrated cannula. Visual analysis of the parabolic-tip cannula showed complete resistance to entrainment whereas the fenestrated-tip had partial entrainment in 90% and 87% of the over-pumping and hypovolemic studies, respectively. We conclude that future pediatric VAD designs may benefit from incorporating the parabolic-tip inflow cannula design in order to maximize unloading of the left ventricle in ideal and non-optimal conditions.

Keywords

mechanical circulatory support; rotary blood pump; inflow cannula; pediatric ventricular assist device

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Introduction

With approximately 36,000 new cases each year in the United States, congenital heart disease is the most frequent birth defect in children.¹ In addition, pediatric cardiomyopathy is a very serious disorder leading to end-stage heart disease with an incidence of 1.13 cases per 100,000 children in the United States.² Some of these patients will require a heart transplantation, but with a waiting list mortality rate of 31% at 6-months many of these patients would potentially be saved by long-term mechanical circulatory support (MCS).³

Currently the only options for pediatric MCS in the smallest patients ($BSA < 0.7 \text{ m}^2$) are extracorporeal membrane oxygenation (ECMO) and the Berlin Heart® EXCOR®.⁴ ECMO is limited to short term support, as the risk of bleeding and thromboembolism complications are proportional to the support length.⁵ Indeed, the success rate for ECMO as a bridge to transplant in pediatrics is less than that of adults supported ventricular assist devices (VADs).^{6–8} While the pulsatile, paracorporeal EXCOR® has greatly improved patient outcomes as the only U.S. Food and Drug Administration-approved pediatric VAD, approximately 80% of patients experienced a significant adverse event during the Investigational Device Exemption (IDE) study.⁹ A subsequent multicenter, prospective study reported substantial significant adverse events within the 204 patient cohort, namely for major bleeding (44%), major infection (46%), and neurological dysfunction (29%).¹⁰ Additionally, both therapies immobilize or limit patient mobility due to pump size, cannulation strategies, and controller equipment. Therefore, there is increased interest in the development of implantable, continuous-flow VADs for chronic, pediatric MCS.^{4,11,12}

While rotary blood pumps are ubiquitous within the adult population, less attention has been given to the development of similar technology for pediatric support.¹¹ Important to the safety and efficacy of a rotodynamic VAD is the interface between the inflow cannula and ventricle. As rotary VADs actively empty the heart throughout the cardiac cycle with the potential to generate negative inlet pressures, premature occlusion at the inflow can lead to complications including myocardial entrapment, inadequate support, thrombosis, hemolysis, inner wall bruising, ventricular collapse or arrhythmias.^{13,14} Pediatric MCS candidates, with smaller and variable anatomical configurations, may be more susceptible to misalignment and ventricular suction in comparison with current adult cannula designs. Therefore, design of an appropriate inflow cannula is of utmost importance in order to reduce the risk of post-surgical complications.

Methods

Cannula Design

In response to the need for a pediatric-appropriate, left ventricular drainage conduit, a new 5 mm nominal ID inflow cannula was designed and fabricated out of wire spring-reinforced (stainless steel flat-wire) polyurethane consisting of a parabolic-shaped inflow tip, a removable sewing ring, and tapered strain relief. A finger-operated clamping mechanism on the sewing ring provides a variable cannula insertion depth up to 2.9 cm. The parabolic cannula was compared against a similarly constructed bevel-tip and a commercially-available fenestrated cannula (20 Fr DLP shortened, Medtronic®, Minneapolis, MN, USA),

both used for *in vivo* preclinical ovine studies previously (Figure 1).¹⁵ The three cannulae have similar characteristic pressure-flow profiles under static conditions as shown in Figure 2.

Experimental Setup

Juvenile ovine or caprine hearts were obtained from a slaughter-house, cleaned, weighed, and trimmed of their pericardium for use in an *ex vivo* pediatric isolated heart model. A removable sewing ring was fixated to the apex of the left ventricle (LV) using 2-0 pledgeted sutures and a borescope was introduced from the left atrium (LA), secured with 2-0 purse string, through the mitral valve for visualization purposes. The aorta was closed with a 2-0 purse string around ¼" OD tubing with a stopcock to release trapped air within the ventricle. The test cannula was then inserted 2.4 cm past the sewing ring, through a cruciate incision in the myocardium.

The experimental isolated-heart flow loop was setup as seen in Figure 3.¹⁶ The circulating fluid of 40% glycerol in saline (4.9 ± 0.1 cP), a blood analogue, was seeded with neutrally buoyant reflective particles (Amberlite IRA-96, Sigma Aldrich, St. Louis, MO). A constant preload into the ventricle was maintained in the vertically elevated fluid reservoir using an overflow chamber. A centrifugal pump (PediMAG®, Thoratec® Corp, Pleasanton, CA) was used to generate flow through the heart-cannula assembly, and a solenoid pinch-valve (ASCO® Valve Inc., Florham Park, NJ, USA) proximal to the LA inlet was utilized to induce contraction and free wall movement in the ventricle. The left atrial (LAP), left ventricular (LVP), and cannula outlet pressure (COP) were measured using three pressure transducers (648, PCB Piezotronics® Inc., Depew, NY), and a clamp-on flow probe (TS410, Transonic®, Ithaca, NY) was attached at the pump outlet to measure flow rate (Q) through the cannula.

The three cannulae were evaluated using two protocol scenarios to mimic the clinical complications of over-pumping and hypovolemia to assess LV unloading ability. Over-pumping was achieved by continually increasing pump speed (PS), starting at an approximate flow rate of 0.3 L/min. The hypovolemia protocol, representing inadequate blood volume, was performed by gradually decreasing LAP from 20 mmHg to 5 mmHg using a proximal tubing clamp while maintaining a constant PS. The over-pumping protocol was carried out with 7 hearts ($n_{op} = 21$) and the hypovolemic protocol was completed with 5 hearts ($n_{hv} = 15$). Both protocols were executed in normal and misaligned positions to assess positional sensitivity, with misalignment created by fixing the cannula posteriorly approximately 45 degrees.¹⁷

Data Analysis

Acquired data was processed using MATLAB® (MathWorks, Natick, MA) for this study. The percent change in flow rate caused by misalignment, termed as the positional sensitivity index (I_{ps}) was calculated using the following equation:

$$I_{ps} = \frac{Q - Q'}{Q} * 100\%$$

for the maximum flows attained in the over-pumping protocol and flows at certain LAPs in the hypovolemic protocol for each cannula, where Q is the flow rate of a normally aligned cannula and Q' is the flow rate when misaligned.¹⁷ Statistical analysis was performed by one-way and repeated measures ANOVA with Bonferroni *post hoc* tests using SPSS® v23.0 (IBM® Corp, Armonk, NY), with significance assumed at $p < 0.05$.

The boroscopic videos were manually analyzed for ventricular collapse and/or entrainment of the cannula orifice during the study.¹⁷ Equal reduction of the LV wall around the cannula was categorized as “Concentric Collapse”, while entrainment was defined in three categories: partial, gradual, and severe. “Partial Entrainment” is defined as the blocking of only a portion of the cannula orifice, while the remaining is unrestricted to flow. In the event of full entrainment of the cannula orifice, a time-analysis was performed to determine the severity. Cases of full entrainment where the average flow rate fell 10% within a one second interval during the suction event were classified as “Severe Entrainment”, while the rest were considered “Gradual Entrainment”. The average flow rate in these cases was calculated for each time point with all data points half a second before and after in order to capture the full cardiac cycle. If no collapse or entrainment was observed, the experiment was categorized as “No Visible Collapse/Entrainment”.

Results

A total of seven hearts (average mass of 140.6 ± 15.2 g) were processed, prepared and used for the *ex vivo* analysis. Raw data from the over-pumping and hypovolemic protocols were processed in MATLAB® in order to calculate the positional sensitivities of the cannulae. Figure 4 is a representative isolated heart experiment showing the hemodynamic performance of each cannula in both protocols in the normal and misaligned state.

Positional Sensitivity

The maximum flow rates and calculated I_{ps} values for the over-pumping protocol are summarized in Table 1. While there was no significant difference in flow rates when normally aligned, there was a significant drop in flow rate for the bevel cannula in comparison to the other two cannulae (p -value < 0.001) when misaligned. Correspondingly, there was no significant difference in I_{ps} between the fenestrated and parabolic cannula, and both were significantly less sensitive to placement position than the bevel cannula (p -value < 0.001).

Likewise, the resultant hypovolemia I_{ps} values across preload pressures for each cannula are shown in Figure 5. The bevel-tip cannula was found to be significantly different than the parabolic-tip cannula at each preload pressure (p -value < 0.001), while no significant difference in positional sensitivity was found between the parabolic-tip cannula and the fenestrated-tip cannula ($p = 1.000$).

Borescope Results

Manual inspection of the ventricular borescope images was performed for each test in the over-pumping and hypovolemic protocols. Multiple cases led to both a concentric collapse and a partial entrainment assessment. In those cases, that experiment was tallied under both

conditions, therefore leading to values over 100% for a particular cannula. The visual example in Figure 6 shows the difference between each cannula in the normally aligned state and the misaligned state. Entrainment and ventricular collapse observations were made from these images, which are summarized in Figure 7. Also in this study, there were six separate instances where at least one of the neutrally buoyant visualization particles were noted to be resting on the caged area of the fenestrated-tip cannula.

Discussion

The results from the over-pumping protocol, performed similarly to clinical echocardiography ramp studies, and hypovolemia protocol indicated that the newly developed parabolic cannula performed significantly better than the bevel cannula. The positional sensitivity results for both protocols suggest that the bevel cannula has a narrow optimal operating window to unload the ventricle, which may explain the complications experienced in prior preclinical *in vivo* pediatric LVAD implantations.^{18,19} Therefore, those complications may be alleviated through the use of the parabolic or fenestrated cannulae, which have a lower sensitivity to misalignment within the ventricle.

Visual analysis of the boroscopic images suggests that there may be subtle differences between the parabolic and fenestrated tip geometry, specifically during misalignment. While a clear and open path was observed for the parabolic cannula prior to any subsequent event, the fenestrated cannula had one or more cage inlets blocked by the ventricular wall in 90% of over-pumping and 87% of hypovolemic studies. This partial entrainment of the fenestrated cannula may lead to damage of the myocardium or hemolysis. Additionally, there were six separate observations of particles resting on the caged portion of the fenestrated cannula which indicates stagnation risk and may be associated with thromboembolic consequences.

The ability to visualize and quantify ventricular ‘suck-down’ makes this a reasonably simple and accurate method for assessing cannula performance, but there are several limitations to this *ex vivo* isolated heart setup described in detail by Bachman et al.¹⁷ Most notably, it is impossible to replicate directly on the benchtop the thrombogenic, thromboembolic, or pannus potential that *in vivo* assessment could provide. The addition of the new solenoid pinch valve cycling at 1.0 Hz (60 beats/min) to control LV preload induced measurable pulsatility (unsteady flow) and led to visible contraction of LV chamber. This dynamic, ‘pulsing-heart’ configuration allowed for the observation of partial or incomplete suction events. While still not a true beating-heart preparation, this is an improvement over the previous static setup.^{16,17}

Ultimately, this experiment showed that the parabolic cannula design is significantly superior to the bevel cannula in completely unloading the LV, and avoids the partial entrainment and stagnation zones associated with the fenestrated design. While literature is vague on the criticality of inflow cannula alignment, the efforts towards VAD suction detection algorithms and automatic speed controllers allude to the frequency and severity of complications associated with non-optimal unloading of the left ventricle.^{20,21} The use of entrapment resistant and position insensitive pump inlet cannulae may reduce intermittent

suction episodes that necessitate speed reductions. This, in part, has served as a basis towards the development of ‘beak’, ‘corona’, and ‘trumpet’ designs with varied success due to thrombosis or thromboembolic complications related to insertion depth rather than inlet tip geometry.^{22–24}

With a reinforced parabolic inlet entrance, this cannula combines the efficiency and flow characteristics of standard ‘stovepipe’ designs, while providing secondary flow paths similar to the fenestrated venous drainage cannula. The novel parabolic-tip cannula is defined by a combination of features including a removable sewing ring for unobstructed visualization, a radiopaque tip to ease myocardial insertion, and a nitinol spring clamp for tool-less depth adjustment. These additions are highly significant for pediatric VADs, as variability in myocardium thickness and chamber geometry between patients would hinder optimal placement with only a single, fixed cannula available. The parabolic cannula allows for this versatility from patient to patient while maintaining optimal flow out of the ventricle.

Conclusion

These studies reinforce the importance of cannula placement for avoiding premature ventricular suction during assisted circulation, and the influence of inflow tip geometry on mitigating the effects of inlet obstructions. The novel parabolic-tip, adjustable depth, pediatric inflow cannula was insensitive to positional placement and enabled maximum unloading of the left ventricle. This information can help guide future pediatric and adult VAD inflow cannula designs to reduce complications during chronic, continuous-flow mechanical circulatory support.

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Figure 1.
The three pediatric inflow cannulae and respective tip geometries (insets) under consideration: the (A) bevel-tip and (B) fenestrated-tip inflow cannulae with fixed-depth sewing rings, and the (C) novel parabolic-tip inflow cannula with the adjustable depth sewing ring.

Figure 2.
Experimentally derived static characteristic pressure-flow (H-Q) curves for the three cannulae using an acellular 40% glycerol/saline solution ($\mu = 4.6$ cP).

Figure 3. (A) Schematic of the modified *ex vivo* isolated-flow loop used to assess cannula performance (aortic vent not shown) and (B) an image of the *ex vivo* flow loop in the normally aligned state.

Figure 4.

Sample data set from one experiment showing cannula performance as measured by achievable flow rate under both protocols. All three cannulae perform similarly with (A) increasing pump speed or (B) decreasing pre-load, however the bevel-tip had a marked drop in flow rate when misaligned (C, D).

Figure 5.

Positional sensitivity results of the three cannulae in the hypovolemic protocol ($n_{hv} = 15$).

Data presented as mean $\pm$ standard error of the mean. The bevel cannula was significantly more sensitive to positioning within the ventricle compared to the fenestrated and parabolic cannulae. ^aBevel v Fenestrated $p < 0.001$, Bevel v Parabolic $p < 0.001$, Fenestrated v Parabolic $p = 1.000$;

Figure 6.

Representative intraventricular images of the normally aligned cannulae (top) and the misaligned cannulae (bottom) from the boroscope. The bevel, fenestrated, and parabolic cannulae are shown to have no obstructions with normal placement (**A,C,E**). However, while all cannulae are facing the LV free-wall when misaligned, the bevel and fenestrated tips are prone to premature myocardial entrapment leading to (**B**) severe or (**D**) partial occlusion of cannula inlet indicated by the arrows. In contrast, the parabolic cannula in the misaligned state (**F**) remains unobstructed.

Figure 7.

Occlusion modality results of the left ventricle as determined by intraventricular imaging and flow rate analysis. In summary, the bevel cannula was severely dependent on intraventricular alignment, the fenestrated cannula was resistant to full entrainment, while the parabolic cannula showed resistance to all forms of premature ventricular suction.

Table 1

Positional sensitivity results for the three cannulae using the over-pumping protocol ($n_{op} = 21$). Data presented as mean $\pm$ standard error of the mean.

	<u>Cannula Type</u>			<i>p</i>
	<i>Bevel</i>	<i>Fenestrated</i>	<i>Parabolic</i>	
<u>Maximum Flow Rate (L/min)</u>				
<i>Normal Alignment</i>	1.27 ± 0.03	1.25 ± 0.04	1.28 ± 0.04	0.822
<i>Misaligned</i>	0.63 ± 0.07	1.18 ± 0.03	1.19 ± 0.02	<0.001 ^a
<u>Ips (%)</u>	49.9 ± 2.2	4.7 ± 2.2	6.7 ± 1.8	<0.001 ^b

^a Bevel v Fenestrated $p < 0.001$, Bevel v Parabolic $p < 0.001$, Fenestrated v Parabolic $p = 1.000$;

^b Bevel v Fenestrated $p < 0.001$, Bevel v Parabolic $p < 0.001$, Fenestrated v Parabolic $p = 1.000$;