Hemodynamic effects of implanting a unidirectional valve in the inferior vena cava of the Fontan circulation pathway: an in vitro investigation

Arvind Santhanakrishnan,1 Kevin O. Maher,2,3 Elaine Tang,4 Reza H. Khiahani,1 Jacob Johnson,1 and Ajit P. Yoganathan1
1The Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia; 2Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; 3Department of Pediatric Cardiology, Children’s Healthcare of Atlanta, Atlanta, Georgia; 4School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia

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Santhanakrishnan A, Maher KO, Tang E, Khiahani RH, Johnson J, Yoganathan AP. Hemodynamic effects of implanting a unidirectional valve in the inferior vena cava of the Fontan circulation pathway: an in vitro investigation. Am J Physiol Heart Circ Physiol 305: H1538–H1547, 2013. First published September 6, 2013; doi:10.1152/ajpheart.00351.2013.—The Fontan surgical procedure used for treating patients with single ventricle congenital heart disorders results in a total cavopulmonary connection (TCPC) of the vena cavae to the pulmonary arteries (PAs). Sluggish TCPC flow and elevated hepatic venous pressures are commonly observed in this altered physiology, which in turn can lead to long-term complications including liver congestion and cirrhosis. The hypothesis of this study is that placement of a unidirectional valve within the inferior vena cava (IVC) will improve hemodynamics of the Fontan circulation by preventing retrograde flow and lowering hepatic venous pressure. An in vitro experimental setup consisting of an idealized TCPC model with flexible walls was used for investigation, and a bovine venous valve was inserted in the IVC below the TCPC. Pressure fluctuations were introduced in the flow through the model to simulate venous pulsatility. Hemodynamics of baseline and valve-implanted conditions were compared across total caval flows ranging from 1.0 to 2.5 l/min with varying caval flow distributions. The results indicated that valve closure occurred for 15–20% of the total cycle, with consequent reduction in the upstream hepatic venous pressure by 5 to 10 mmHg. Energy loss (EL) through the TCPC was lowered with valve implantation to 20–50% of baseline, occurring across all flow conditions considered with mean caval and PA pressures greater than 10 mmHg. The results of this in vitro modeling suggest that IVC valve placement has the potential to improve hemodynamics in the Fontan circulation by decreasing hepatic venous hypertension and EL.

Fontan circulation; transcatheter valve; hepatic venous hypertension; in vitro Fontan model; single ventricle

APPROXIMATELY 2,000 CHILDREN are born every year in the United States with a series of congenital heart malformations that result in a single ventricle (SV) physiology. Surgical palliation is typically the preferred method of treatment for these patients as an alternative to neonatal cardiac transplantation. The common endpoint of SV surgical palliation, known as the Fontan procedure (7), consists of using the SV for systemic circulation and routing venous return from the inferior vena cava (IVC) and superior vena cava (SVC) directly to the pulmonary arteries (PAs) (4, 5). Despite favorable short-term outcomes and lowered mortality rates (1, 13, 14, 17, 19), numerous long-term complications have been reported (8) including ventricular dysfunction and limited ventricular power (28), increased pulmonary vascular resistance (4), arrhythmias (6), severely diminished exercise capacity (21, 24, 31), protein losing enteropathy (22), and hepatic complications (4, 9). Although considerable advances have been made in understanding total cavopulmonary connection (TCPC) hemodynamics (16, 18, 20, 29, 30) and in pre-operative surgical planning (26), therapies for improving cardiac hemodynamics and averting end-stage complications in the growing population of Fontan patients are currently lacking.

Of specific interest to this study are the effects of Fontan circulation on the liver and gastrointestinal (GI) tract. The altered series arrangement of the systemic and pulmonary circulations in the Fontan patient, together with the lack of a functional right heart to pump blood to the lungs, predisposes the systemic veins to higher pressures and in turn elevates hepatic venous pressure. In the absence of a right ventricle, the flow to the lungs through the TCPC relies on (1) elevated caval pressures (15), (2) venous pulsatility from single ventricular pump function or via a terto (25), (3) negative intrathoracic pressures during inspiration (10, 11), and (4) peripheral pumping provided by abdominal and leg muscle contraction (9a). The interactions between venous pulsatility and respiratory intrathoracic pressure fluctuations effectively result in sluggish flow through the TCPC with retrograde flow occurring during expiration (10, 11). It is imperative that the IVC and hepatic venous pressures must be lowered to decrease the risk of liver and GI complications in the Fontan circulation, and this is the focus of the research presented herein.

In this study, we hypothesize that inserting a unidirectional valve in the IVC of the Fontan circulation will aid in alleviating IVC/hepatic venous hypertension by arresting retrograde flow in the TCPC. It is expected that when the IVC valve closes on account of flow reversal (away from lungs), the kinetic energy of the retrograde flow will be stored as potential energy in the compliant venous vessel walls. This energy can be used to effectively augment the antegrade portion of the flow and minimize overall energy losses occurring in the TCPC. The above hypothesis is tested using an in vitro experimental circuit of the Fontan circulation. As a part of this effort, this study also will investigate the use of minimally invasive transcatheter valve based therapy in the Fontan circulation.
MATERIALS AND METHODS

TCPC model and chamber. To assess the hemodynamic changes obtained from implanting a valve at the IVC with quasi-physiologic representation of compliant venous walls, a flexible walled TCPC model was used in this study. The two-dimensional model measured 160 mm × 220 mm in cross-section with a wall thickness of 1 mm and internal diameter of 20 mm (Fig. 1) and was prototyped using shore hardness 27A Tangoplus elastomeric material (Spectrum Plastics Group). The TCPC model was immersed in a hydraulic chamber that measured 170 mm × 250 mm in cross-section and height of 75 mm with a sealable top wall. The hydraulic chamber demarcated the intrathoracic space within which the flexible TCPC model was placed. The hydraulic chamber was filled with water and sealed to maintain an average static pressure of 3–5 mmHg when the TCPC model was primed and filled with fluid in the pressure range of 10–16 mmHg.

Mock circulatory loop. An in vitro experimental circuit of the Fontan circulation was developed for this study (Fig. 2A). A submersible centrifugal pump was immersed in a lower fluid-filled reservoir (at ground level), which was used to maintain a constant pressure head in an upper reservoir located at a height of 1.8 m above the TCPC model. A programmable piston pump (Model SPL39891; ViVitro Labs, Victoria, British Columbia, Canada) was connected near the reservoir before the bifurcation of inflows (flow to SVC and IVC) to provide pressure fluctuations and retrograde flows seen in the Fontan circulation (11, 16). The conduit containing the IVC valve, as described below, was positioned outside and upstream (caudal) of the TCPC enclosing chamber. Saline was used as the working fluid medium to maintain the Melody valve tissue property without degradation due to dehydration (osmotic transport) or fixation of leaflets. Other than the valve holding conduit, rigid tubing was used for all circuit connections (except needle valve locations described below).

A ball valve was used to control bulk flows and pressures. To provide finer resistance control for tuning IVC and PA hemodynamics, needle valves were used downstream of the ball valves. Each needle valve was mounted onto a small piece of collapsible latex tubing (35A shore hardness) of 20 mm internal diameter. The total inflow (SVC + IVC) was varied from (in l/min) 1, 1.5, and 2.5 across experiments. The caval flow distribution was varied in the experiments from 70% IVC (and 30% SVC), 60% IVC (and 40% SVC), and 50% IVC (and 50% SVC). The flow distribution at the outflow was maintained constant at 45% ± 5% left pulmonary artery (LPA) across all experiments reported in this article. At the 1.5 l/min total inflow condition, the pressures at IVC, SVC, LPA, and right pulmonary artery (RPA) were varied in two ranges, 10–15 mmHg and 5–10 mmHg, for assessing the range of applicability of the IVC valve design selected for this study.

IVC valve and implantation. The Medtronic Melody transcatheter pulmonary valve (Fig. 2B) was used for this study; this is a bovine jugular venous valve mounted on a stent and used for treatment of PA conduit stenosis or regurgitation. A balloon-in-balloon (BIB) catheter delivery system with a retractable polytetrafluoroethylene (PTFE) sheath covering was used for the purpose of deployment. The system consisted of a 22-mm outer balloon and 11-mm inner balloon with a 22 French delivery sheath. A Melody valve was mounted onto the balloon system, and the stent was crimped to roughly 6 mm diameter. The inner and outer balloons were pressurized to 4 atm and 2 atm, respectively, to re-expand the Melody valve to ~22 mm outer diameter. The Melody valve was delivered within a latex rubber conduit (35A shore hardness) of 20 mm internal diameter and length 20 mm. In the baseline (no valve) condition, a similar rubber conduit was used in place of the valved conduit at the same location.

Instrumentation and data acquisition procedure. Hemodynamics of the in vitro Fontan circulation model were acquired through measurements of static fluid pressures and flow rates at multiple locations as indicated in Fig. 2A. Disposable Deltran absolute pressure transducers (DPT-200; Utah Medical Products, Midvale, UT) were used for pressure measurements. Transducers were located upstream (caudal) and downstream (cephalad) of the IVC valve (when present), and in the SVC, RPA, and LPA. The pressure upstream (or caudal to) the IVC valve is referred to as the hepatic venous pressure (P_hv). A custom fluid-filled catheter was used to record TCPC junction pressure (P_TTCP), centrally positioned in the cross-section of the intersection of IVC, SVC, LPA, and RPA. Two electromagnetic flow probes (Model 300A; Carolina Medical Electronics, East Bend, NC) were used for measurement of the SVC and IVC flows. The IVC flow probe was positioned upstream (caudal) of the IVC valve location in the circuit. Two ultrasonic flow probes (Model ME PXN; Transonic Systems, Ithaca, NY) were used for measurement of the LPA and RPA outflows. Two data acquisition systems (NI USB-6251; National Instruments Corporation, Austin, TX) were used to acquire data synchronized with the piston pump. An in-house LabView program was used for recording data, trigger generation, synchronization between data acquisition systems, and the piston pump. The piston was set to move in a sinusoidal motion with a period of 1 s to generate characteristic venous flow and pressure fluctuations in the system.

For the purpose of ascertaining that relative comparisons between baseline and with valve hemodynamics were valid, it was assumed that transcatheter implantation of the valve in the IVC in vivo would not result in immediate instantaneous alterations to the flows through the vena cavae and PA resistances. For translating this in vitro, we considered steady flow conditions where the valve operation was not expected to alter the hemodynamics through the TCPC model com-
pared with baseline (steady) flow. In comparison with the baseline steady flow conditions, the flows through SVC, IVC, RPA, and LPA were matched to within ±0.25 l/min and the pressures at IVC valve (upstream/caudal), SVC, RPA, and LPA were matched to within ±1 mmHg, across all conditions investigated with valve in this study. The baseline case and the IVC valve had the same conduit material and construction.

For each pulsatile flow experiment, hemodynamic data (pressures and flows) containing 60 cycles of piston motion were acquired, and results were averaged across cycles. The cycle-to-cycle variation of acquired flows and pressures, calculated as root mean square (RMS) of fluctuations from mean value, were less than 2% across all experiments in this study.

Valve kinematics. To characterize the closing behavior of the IVC valve, video sequences of the valve were acquired en face using a viewing chamber located below or caudal to the valve. The videos were recorded at 30 frames/s using a 3.3 megapixel Sony Handycam camcorder. The resulting video was exported as an image sequence. The start of piston motion, coincident with the initiation of pulsatile flow through the system, was noted in the video through audio-visual cues. This was used to identify the starting frame of the first cycle, and individual frames from 5 consecutive cycles (each with 1-s period) were identified and grouped separately. Two measures of valve closure were obtained from manual inspection of images: 1) total time of valve closure: equivalent to number of frames where the valve is fully closed and 2) starting point of valve closure: identified as the first frame in a cycle where the valve is fully closed. Both these metrics were nondimensionalized with the total cycle time, which were then averaged across 5 consecutive cycles.

Hemodynamic characteristics for comparison. To compare the performance of the IVC valve, the following hemodynamic characteristics were used: hepatic venous pressure (PHV) measured at a location upstream (i.e., below or inferior) of the valve; TCPC junction pressure (P_{TCPC}) measured using the fluid-filled catheter; and instantaneous TCPC flow rate calculated as the difference between sum of inflows and sum of outflows: Q_{TCPC} = (Q_{IVC} + Q_{SVC}) - (Q_{LPA} + Q_{RPA}) (Eq. 1).

Cycle-averaged hemodynamic energy loss (EL) was evaluated using Eq. 2: EL = \sum \left( P_{\text{inlet}} + \frac{1}{2} P_{\text{inlet}}^2 \right) Q_{\text{inlet}} - \sum \left( P_{\text{outlet}} + \frac{1}{2} P_{\text{outlet}}^2 \right) Q_{\text{outlet}}

Q_{\text{inlet}} = \left( Q_{\text{IVC}} + Q_{\text{SVC}} \right), Q_{\text{outlet}} = \left( Q_{\text{LPA}} + Q_{\text{RPA}} \right)

Q_{\text{inlet}} = \left( Q_{\text{IVC}} + Q_{\text{SVC}} \right), Q_{\text{outlet}} = \left( Q_{\text{LPA}} + Q_{\text{RPA}} \right)

Percentage reduction in energy loss was computed as the difference in energy loss between baseline and with valve case, normalized by baseline energy loss.

RESULTS

Hemodynamic changes after valve implantation. Figures 3 and 4 show the comparative hemodynamics of valve implanted and baseline cases for a total inflow of 2.5 l/min with mean IVC,
SVC, and PA pressures in the range of 10–15 mmHg, at 70/30 IVC/SVC flow distribution. Inclusion of the IVC valve within the circuit resulted in a reduction of the pressure before valve (equivalent to hepatic venous pressure in our model) by over 10 mmHg for ~20% of the cycle (see Fig. 3A for 200 ms-400 ms). The pressure drop across the valve was less than 1 mmHg (P_{HV}-P_{IVC}) under steady flow conditions across all inflows considered in this study, indicating minor resistance offered by valve implantation to the inflow. The RPA outflow (Fig. 3B) following valve implantation (cycle averaged Q_{RPA} = 1.6 l/min) was augmented by 23% compared with the baseline case (cycle averaged Q_{RPA} = 1.3 l/min). The nature of the RPA flow augmentation compared with that of the LPA (Fig. 3B) suggests that the RPA outflow is primarily derived from the IVC inflow within our in vitro model. The flow through the TCPC model (Fig. 4A), calculated using Eq. 1, was augmented with valve implantation by 50% (cycle averaged Q_{TCPC} = 0.82 l/min) compared with the baseline case (cycle averaged Q_{TCPC} = 0.54 l/min). The TCPC junction pressure was increased with valve insertion post closure (Fig. 4B), corresponding to the above increase in TCPC flow with valve implantation.

Effect of changing inflow conditions. For a constant total inflow with IVC, SVC, and PA pressures in 10–15 mmHg range, altering the IVC/SVC flow distribution did not result in changes to the magnitude and extent (of total cycle duration) of hepatic venous pressure reduction and TCPC junction pressure augmentation following valve closure (Fig. 5). In comparison, lowering the total caval inflow resulted in lowering the magnitude of hepatic venous pressure reduction (Fig. 6, A and C). The TCPC junction pressure augmentation following valve closure was also increased with higher total inflow (Fig. 6, B and D).

Overall, the energy loss through the TCPC model was lowered with valve implantation compared with baseline conditions (see Table 1), across all inflows and inflow distributions (IVC/SVC) considered in this study. The percent energy loss reduction obtained with valve implantation, averaged across all flow rates, was 33%.

Valve kinematics. The average duration of valve closure, normalized to cardiac cycle, ranged from 15% to 25% (Fig. 7A). The valve closure duration was lowest for a total caval inflow of 2.5 l/min, whereas inflows of 1 l/min and 1.5 l/min did not show any noticeable changes in closure characteristics. Although hemodynamic observations showed that 2.5 l/min inflow provided a larger hepatic venous pressure reduction compared with 1 l/min, the duration of valve closure was inversely affected by the inflow magnitude. With reference to the caval flow distribution, the starting point of valve closure (Fig. 7B) was most delayed for 50/50 inflow distribution across total inflows of 1 l/min and 1.5 l/min, compared with 70/30 inflow distribution for total inflow of 2.5 l/min.

Effect of changing mean vessel pressure range. For a total inflow of 1.5 l/min and lower mean IVC, SVC, and PA pressures in the range of 5–10 mmHg, the IVC pressures for baseline and with valve showed more temporal variability across all flow distributions (Fig. 8). The 50/50 inflow (IVC/SVC) distribution showed the least reduction in hepatic venous pressure and reduction in TCPC junction pressure (Fig. 8, A and B), compared with 60/40 IVC/SVC and 70/30 IVC/SVC inflow distributions. Energy losses were increased with valve implantation across all flow distributions compared with the corresponding baseline conditions (Table 2).
DISCUSSION

The overall results of this study demonstrated the potential applicability of IVC valve therapy in the Fontan circulation, for the purpose of lowering hepatic venous pressure by arresting retrograde flow occurring in the IVC. The performance of the unidirectional valve in the IVC of Fontan circulation provided reduction of hepatic venous pressure by 5–10 mmHg (for ~20% of the cardiac cycle) and 20–50% reduction in hemo-

Fig. 5. Effect of changing inflow distribution on IVC pressure and TCPC junction pressure for total inflow of 2.5 l/min: A and C are for 60% IVC inflow proportion, and B and D are 50% IVC inflow proportion.

Fig. 6. Effect of changing total inflow on IVC and TCPC hemodynamics: 1.5 l/min (A and B) and 1 l/min (C and D).
dynamic energy losses over the cardiac cycle. No study to date has examined the hemodynamic changes obtained from simulating extrathoracic valve implantation for alleviating hepatic venous hypertension in the Fontan circulation. The study presented in this article represents the first effort in this important direction. The use of the in vitro model as developed in this study allows for systematic characterization of the hemodynamic effects of valve implantation to identify the most optimal conditions for this therapy. Furthermore, the Fontan flow circuit facilitated a controlled study to compare valve implantation with baseline circulation and visualization of valve kinematics; both these aspects cannot be easily evaluated in animal studies.

Several caval flows and distributions were examined to assess the comparative hemodynamics with and without implantation of the IVC valve. For intravenous pressures (in SVC, IVC, and PAs) greater than 10 mmHg and total caval inflows in the range of 1 to 2.5 l/min, the inclusion of the IVC valve produced a marked reduction in hepatic venous pressure for 10 – 20% of the cardiac cycle. Furthermore, reduction in energy loss through the TCPC was observed with the valve, with augmentation of TCPC flow due to increase in driving pressure at the TCPC junction. The energy loss calculated here includes both potential (static pressure) and kinetic (fluid dynamic) energetic contributions. Closure of the IVC valve prevents retrograde flow and effectively lowers the energy loss through the TCPC by only allowing antegrade flow. The underlying mechanism of the IVC valve is in storing the kinetic energy of the retrograde flow within the compliant TCPC above the valve. This is evidenced by the higher pressure in the TCPC following valve insertion, which indicates more volume (less reversal of flow) in the TCPC, consistent with the augmentation of flow through the PAs. Although changing caval distribution did not noticeably impact TCPC hemodynamics between baseline and with IVC valve cases, the TCPC junction pressure increased with increasing total caval inflow. This suggests that the valve operation is affected by the amount of available inertia in the flow, controlled via inflow magnitude. The reduction in energy loss following valve implantation increased with increasing caval inflow from 1 l/min to 2.5 l/min, possibly due to more interaction of the caval flows at the TCPC junction. Finally, the energy losses with valve placement were increased with lowering the mean pressures (IVC, SVC, PAs) to less than 10 mmHg. This indicates that the benefits of this therapy may not occur in this lower range of pressures.

The Melody valve is currently approved by the Food and Drug Administration (FDA) in the United States for compassionate use in pediatric or adult patients with a dysfunctional right ventricular outflow tract either due to either a regurgitant or stenotic pulmonic valve. This is a high-pressure system compared with typical pediatric Fontan venous circulation. We expected that there would be a design bandwidth to adapting the Medtronic Melody valve for modifying hemodynamic characteristics within a lower pressure system such as the Fontan circulation. The results of the study show that the valve functions to lower hepatic venous pressure and energy losses for mean SVC, IVC, and PA pressure range of 10 – 15 mmHg. This range is typical in Fontan patients, with chronic elevation of central venous pressure (CVP). Patients with higher filling pressures are at the highest risk for developing long-term hepatic/GI complications and may benefit the most from placement of a valve in the IVC.

It is important to note that the valve implantation investigated herein is not entirely a new concept. Fontan and Baudet (7) used an aortic valve homograft at the anastomosis of right atrial appendage with the proximal RPA, and a pulmonary homograft in the IVC at the junction with the right atrium, in

<table>
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<th>Flow Split IVC/SVC [%]</th>
<th>1 l/min</th>
<th>With Valve</th>
<th>1.5 l/min</th>
<th>With Valve</th>
<th>2.5 l/min</th>
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<tr>
<td>70/30</td>
<td>3.8</td>
<td>2.6</td>
<td>8.2</td>
<td>6.5</td>
<td>14.9</td>
<td>11.8</td>
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<tr>
<td>60/40</td>
<td>4.0</td>
<td>1.3</td>
<td>7.3</td>
<td>5.6</td>
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<tr>
<td>50/50</td>
<td>4.6</td>
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IVC, inferior vena cava; SVC, superior vena cava; PA, pulmonary arteries.

Table 1. Comparison of power losses [mW] for baseline and with valve experiments for average IVC, SVC, and PA pressures in the range of 10 – 15 mmHg

Fig. 7. Kinematics of the IVC valve as a function of changing inflow conditions: total time of valve closure (A) and starting point of valve closure normalized by total cycle time (B). Error bars indicate the SD across 5 consecutive cycles of 1-s period. $t_{\text{start}}$, starting point of valve closure; $t_{\text{closed}}$, total time of valve closure; $T_{\text{cycle}}$, time period of the cycle (1 s).
the original Fontan procedure for the treatment of tricuspid atresia. Using right atrial angiography, they observed that the pulmonary valve homograft arrested reverse flow. Baslaim et al. (2, 3) used a Medtronic Contegra xenograft in surgical studies as the extracardiac baffle for the TCPC and reported post-operative improvements including continuous antegrade flow in the IVC and minimal flow reversal in the hepatic veins. Detailed hemodynamic evaluation of the valve function was not presented in either of these studies. However, these results were encouraging and supported examining the current hypothesis of using a bovine venous valve to lower hepatic venous pressures. It must be noted that the current study design is distinguished by valve placement in the subdiaphragmatic position (above hepatic venous confluence) as compared with the previous efforts. This particular extrathoracic placement minimizes the interaction of the valve with the highly unsteady flow patterns that can be expected at the TCPC junction and specifically targets the functionally challenged IVC hemodynamics near the liver and GI tract (11). In vivo valve placement in the subdiaphragmatic position is expected to benefit from the changes in intrathoracic pressure associated with spontaneous ventilation. However, the clinical applicability of subdiaphragmatic valve insertion will need to be evaluated in vivo using an animal model. It must be noted that valve implantation in Fontan circulation could lead to thrombus formation, and this

Table 2. Comparison of power losses [mW] for baseline and with valve experiments for total inflow of 1.5 l/min and average IVC, SVC, and PA pressures in the range of 5–10 mmHg

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<th>Flow Split IVC/SVC [%]</th>
<th>Baseline</th>
<th>With Valve</th>
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<tr>
<td>70/30</td>
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is outside the scope of the current study. The thrombosis potential of implanting the IVC valve used herein needs to be investigated using in vivo studies.

The principal hemodynamic causes for deterioration of the GI tract and the liver in the Fontan physiology/circulation are not well understood. Hepatic congestion in the Fontan circulation could be expected to arise primarily due to the elevated CVP conditions in the proximity of the TCPC junction. A recent in vivo study (23) showed that CVP directly correlated with the degree of liver stiffness. Although elevated CVP is necessary for pulmonary blood flow, it can simultaneously lead to congestion of the hepatic circulation, thereby leading to complications such as hepatocellular carcinomas, cardiac cirrhosis, and liver failure (4, 9). Furthermore, venous vasculature in the abdominal area, including the portal venous system, can also be negatively impacted due to venous hypertension. The caval blood flow is driven primarily through a passive pressure gradient-based mechanism in the Fontan circulation due to the absence of a right ventricle. Flow reversals in the IVC have been previously observed in the Fontan circulation and have been attributed to both venous pulsatility and intrathoracic pressure fluctuations (9a, 11). This patient population may benefit from removal of the retrograde IVC flow and decrease in venous pressures, aiming to prevent or delay the onset of liver and GI tract complications. Implantation of a unidirectional valve near the hepatic venous confluence within the IVC provides a direct means to achieve this goal. The practical appeal of the proposed therapy is that it does not require an external power source and can be implanted using a minimally invasive approach in the catheterization laboratory.

The clinical significance of this study is that a minimally invasive transcatheter valve therapy has the potential to improve the hemodynamics of the growing population of Fontan patients that are at high risk for developing hepatic and GI tract complications. Albeit externally powered circulation using ventricular assist devices (VADs) have been recently proposed as a method to preemptively address systemic venous hypertension and diminished CO shortcomings of the Fontan palliation (27), two major practical implementation concerns can be identified at the present time. Currently available VADs that can be used directly or adapted for Fontan circulation are typically restricted for short-term use as a bridge device before transplantation, and not for long-term use or destination therapy. Furthermore, commercially available VADs require invasive implantation that do not grow and adjust with the patient, which poses challenges for early/initiation stage implantation. In comparison with VADs with artificial propeller elements, the natural environment of the circulation will only be minimally disturbed with the introduction of a stented biological valve. Finally, the results of this investigation are encouraging to develop more hemodynamically efficient transcatheter valve designs, based on pediatric physiology, to extend the range of applicability to the venous circulation of pediatric patients with low flow, low pressure conditions.

**Limitations.** An important limitation of the study lies in the amplitude of pressure fluctuations imposed for incorporating venous flow pulsatility. The TCPC model was the only compliant component used in the construction of the in vitro flow loop, and all other parts were not distensible. As a result, our circuit had a larger pulmonary vascular resistance compared with in vivo Fontan physiology. This resulted in amplifying the pressure fluctuations and retrograde flow rates recorded in the study. We were not able to match all the relevant physiological parameters in the study due to lack of arterial and venous capacitance vessels observed in vivo. We did not use compliance chambers for matching in vitro model compliance to in vivo Fontan physiology, and this limitation of our study will be addressed in future work. Our goal was to simulate Fontan circuit flows and pressures and evaluate the performance of the valve with respect to the baseline case. Consequently, the numerical values of the results reported in this study, including energy loss and hepatic venous pressure reduction, are specific to the in vitro model and cannot be expected to occur exactly within in vivo models. Due to the simplifications underlying the design and construction of our in vitro model, there is a possibility that the results reported herein could have artificially enhanced the benefits of this therapy. In vivo studies of the valve implantation in an animal model are crucial to comprehensively evaluate the precise levels of hemodynamic benefits. However, the trends of reduction in energy loss and hepatic venous pressure with valve implantation compared with baseline case without valve in the actual physiology are expected to be similar to the in vitro observations.

The TCPC geometry was idealized for the purpose of this initial study of the proposed therapy, and the extent of tortuosity and curvature observed in actual patient anatomies were not included. The internal diameters of the IVC, SVC, and PAs used in the model design were within the range observed in Fontan patients (15–20 mm). Altering the model geometry will not impact the relative hemodynamic effects of implanting the valve in terms of hepatic venous pressure reduction in comparison with baseline case. A second limitation was the use of saline as the fluid medium. Saline was used to preserve the leaflet tissue characteristics and maintain functionality without initiating dehydration and/or fixing the valve. The choice of not using glycercine in matching viscosity of fluid medium to blood was dictated primarily due to concerns that prolonged exposure to glycercine could alter the valvular material properties. The pressure field across the valve between using saline and water-glycerine mixture is not expected to be significant. Although saline does not have the same dynamic viscosity as blood, relative comparison of the change in hemodynamics between baseline and valve implantation will be unaffected. Furthermore, the trends observed here with regards to reduction in energy loss with valve implantation would remain unchanged despite the lack of viscosity matching. It is important to note that we did not include respiratory intrathoracic pressure fluctuations and intra-abdominal pressure fluctuations in our in vitro model, and these interactions are expected to affect valve function in relation to implantation position (extrathoracic placement at diaphragmatic level, or intra-thoracic placement). Respiration-induced flow pulsatility causes the bulk of retrograde flow in the IVC of Fontan circulation (9a–11). The simplifications in our in vitro model resulted in a larger level of retrograde flows despite not accounting for respiration. Clinical data describing the isolated effects of venous pulsatility and respiratory pulsatility on pressure fluctuations within the IVC of Fontan circulation are scarce. Quantitative hemodynamic changes due to valve implantation are expected to be different than those demonstrated in this study, upon including intrathoracic (respiratory) and intra-abdominal pressure in the experimental model. These factors will be the subject of future research.
work. However, the relative trends of the results presented herein, comparing baseline case to valve implantation, are expected to be similar. Finally, the compliances of the TCPC model and the intrathoracic chamber enclosing the TCPC were not matched to physiological values. However, the relative comparisons presented in this study between baseline and with valve conditions had the same compliances throughout.

Conclusions

A bovine venous valve was used in the IVC of an in vitro Fontan circulation model to prevent retrograde flow and lower hepatic venous pressure. For mean IVC, SVC, and PA pressures greater than 10 mmHg and caval inflows ranging from 1 to 2.5 l/min, the valve closure resulted in a simultaneous reduction in hepatic venous pressure and a decreased energy loss as compared with baseline conditions. The TCPC junction pressure was increased with valve implantation for these conditions compared with the baseline case. The results of the study demonstrate the applicability of the proposed minimally invasive therapy for improvement of hepatic venous hypertension in the Fontan circulation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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