Unassisted in-vitro simulation of superior cavo pulmonary shunt for evaluation of pathophysiological issue

F. De Gaetano[1], M. Griselli[2] and M.L Costantino[1]
[1] LaBS, Dept. of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, ITALY
[2] Division of Pediatric Cardiac Surgery, Dept. of Surgery, University of Minnesota Masonic Children's Hospital, MN, USA

***Abstract*— In this study, a new in-vitro test bench of the bidirectional superior cavo-pulmonary connection (BCPC), which can mimic realistic conditions, was developed to provide the physician with a platform onto which to test surgical procedures outcomes by acquiring local measurements of the relevant hemodynamic quantities. Using values of resistances and compliance from literature data, a simplified lumped parameters model was designed to fit patients from 2 to 5 years. The mock loop circulation developed in this work was validated by using the in-vivo catheterization data from 20 patients.**

All the parameters were first set to obtain physiological condition. Then four different dysfunctions were mimicked: diastolic dysfunction, systolic dysfunction, cavo-pulmonary intrinsic failure and a complex mix of these failures.

The measured pressure and flow rate showed an excellent correlation with the clinical catheterization data acquired in BCPC. This new in-vitro test bench can be a handy tool capable of providing better insight on how to treat these patients and which devices to employ in different clinical scenarios.

***Keywords*—Bidirectional superior cavo pulmonary connection, in-vitro test bench, paediatric circulation, TCPC.**

I. Introduction

Mechanical circulatory support (MCS) for failing single ventricle physiology is a complex and challenging problem, which has not yet been satisfactorily addressed.

Today, the total cavo-pulmonary connection (TCPC) is performed as the final stage to achieve the so-called "Fontan Circulation", and this is obtained through two- or three-stage strategy for children suffering from a wide range congenital cardiac defects not suitable for two-ventricle repair. The bidirectional superior cavopulmonary connection (BCPC), historically and still inappropriately called "Glenn procedure", remains a fundamental intermediate step for these kinds of patients towards the "Fontan circulation".

Many centres advocate the intermediate palliation with a BCPC to improve the long-term outcome of the Fontan circulation [1], [2]. The advantages of BCPC as primary or second-stage palliative procedure include the relief of the volume load on the single ventricle, improvement in atrioventricular valve regurgitation, avoidance of pulmonary artery distortion after pulmonary artery banding or systemic-to-pulmonary artery shunts and prevention of the possible pulmonary vascular obstructive disease that can be developed with prolonged systemic-to-pulmonary shunting [3].

Clinical data show that the BCPC provides excellent early and midterm palliation, with a low incidence of reoperation [4]–[6].

Nowadays, the perioperative mortality rate has declined to 2%, due to improved patient selection, better adjustment of pulmonary blood flow, and to the refinement of the BCPC [7]. Perfect univentricular physiology is, however, an elusive goal. The TCPC represents the best haemodynamic compromise, but it could result in a cluster of multi-organ complications. Recently, an increasing number of single ventricle patients surviving the various stages of palliation showed a severe deterioration of the haemodynamic state requiring mechanical assist support. In-vitro simulation of the clinical situation, which can mimic realistic conditions [8], would provide the physician with a platform onto which to test surgical procedures outcomes by acquiring local measurements of the relevant hemodynamic quantities. Several models of the single-ventricle Fontan and failing Fontan circulation were developed [9]–[11] but, despite the importance, there is a lack of in-vitro model mimicking the BCPC [12]. Development of an in-vitro test bench reproducing the BCPC may provide more targeted treatment options to solve the underlying causes of failure. The optimal management of patients with single ventricular physiology complicated by pulmonary hypertension and elevated pulmonary vascular resistance (PVR) remains undefined [13]. The test bench developed in this work can be an optimal tool to investigate the best way to manage patients with failing cavo-pulmonary circulation. This in-vitro system is aimed at reproducing the proper haemodynamic conditions.

II. Materials and Methods

In the MCS here described, the BCPC was schematized by using a single ventricle connected both to the lower body (LB) and to the upper body (UB) circulation. The superior vena cava (SVC) connects the UB to the pulmonary circulation, while the inferior vena cava (IVC) connects the LB to the common atrium. The loop is closed by connecting the pulmonary circulation to the common atrium (Fig.1). UB, LB and pulmonary circulation were each one described by a variable linear resistance, compliance, and imposed inertance elements.

These elements allow the replication of the haemodynamics both in physiological and in pathological BCPC patients. The single ventricle was reproduced by using a 15 cc pulsatile VAD (Excor®, Berlin Heart, Germany). The Ikus Driving Unit (Berlin Heart, Germany) was set to give to the VAD the right supply pressure to control the stroke volume, the heart rate and the systolic ratio.

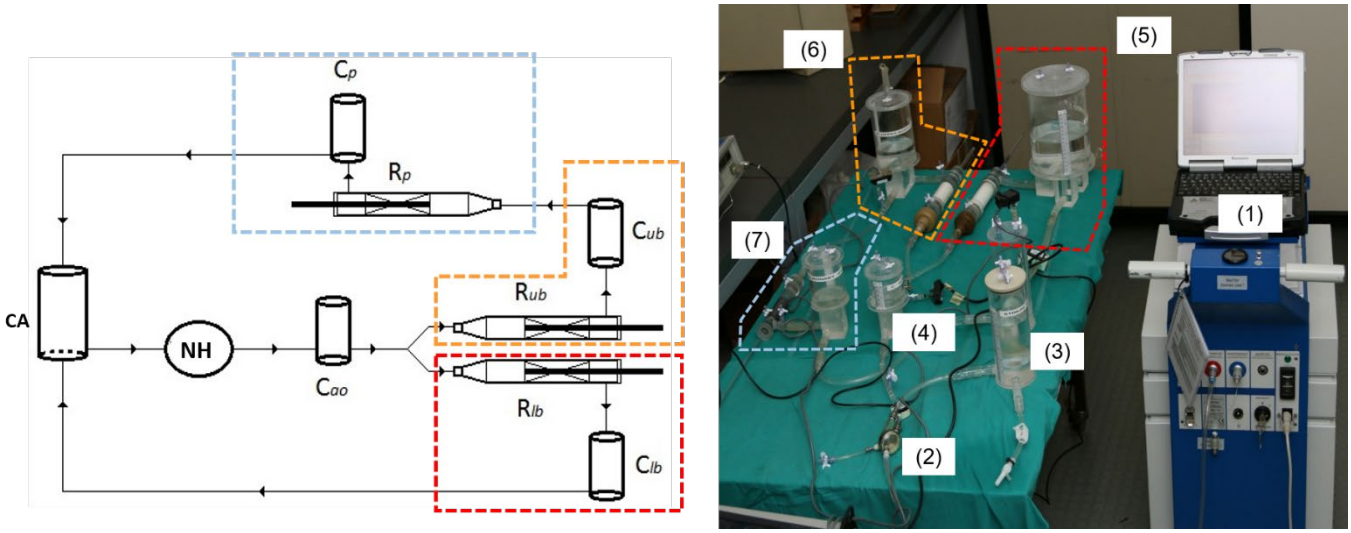

Fig. 1 Sketch (left) and picture (right) of the in-vitro test bench. The test bench is made by the Ikus unit (1), the native heart (NH) obtained using a 15 cc Excor® VAD (2), the common atrium (CA, 3), the aortic compliance (C_{ao}, 4) and the lower body (5), upper body (6) and pulmonary (7) blocks.

With references to the value of resistances and compliance from literature data [14], a simplified lumped parameters model was designed to fit patients from 2 years (BSA = 0.55 m^2) to 5 years (BSA = 0.74 m^2). To verify the reliability of the lumped parameter model in both physiological and pathological conditions, an electrical equivalent of the test bench was implemented in Simulink (Matlab®, Mathworks, MA, USA). It is important to remark that this mathematical model was created only to aid in the construction of the in-vitro test bench and not to support the clinical decision. All the value of the parameters used to mimic the BCPC physiological conditions in 4 years old patients are summarized in Table I. After the validation comparing the mathematical model with in-vivo catheterization performed on 20 patients, the elements of the MCS were built up.

In general, the solution chosen to make up hydraulic resistances consisted in preparing arrays of tubes of small diameter [15] [16]. If a rigid tube was used to build the resistance, the Poiseuille's law would be used to calculate the value of the resistance. It would thus be possible to obtain the desired value of the hydraulic resistance by adding an appropriate number of identical tube elements connected in parallel. With this solution, it is possible to get different values of resistances, but their setting could result quite difficult in replicating both pathological and physiological values with a single component. If a range of different values would need to be simulated, other resistors should be developed, and their dimensions could result quite large.

To overcome this issue, we developed the resistance elements taking into account Darcy's law that describes the fluid flow through a porous medium. Different cylinders with different porosity were 3D printed (3D Printer M2, Makergear, Ohio, USA) using a layer resolution of 50 µm, a nozzle size of 0.35 mm and a brass plate heated at 110°C. The 3D printed cylinders were tested to evaluate permeability. After setting the cross-section area (A) of the resistive element, and knowing the permeability (k), the length (L) was set to obtain the maximum resistance. A, k and L are set and selected to reproduce the values of resistances from literature data using water as working fluid in the test-bench. A sliding stick inserted into the porous cylinder allows setting different values of the resistance. Moving the bar all along the length, the wet area can be increased or decreased reducing or increasing the hydraulic resistance, respectively (Fig. 2).

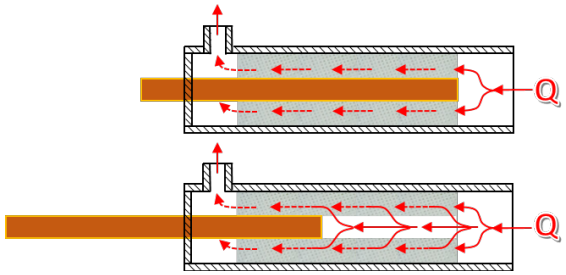

Fig. 2 Sketch of the resistor made by a porous cylinder (in grey) with a sliding stick inside used to modify the value of the resistance. Q is the flowrate that comes from right to left.

The physical solutions to obtain compliances are based on the use of the elastic properties of air. The hydro-pneumatic compliance consists of a tank partially filled with liquid with a volume of air above it. The inertial effects are present in all the types of lumped parameter hydraulic components and cannot be eliminated but rather minimized. Connection tubes are always present in hydraulic circulatory models and are, in general, the most crucial source of inertial effects. The proper choice of the connection tubes dimensions can help in controlling the role of inertial components in the circuit. The MCS was equipped with ¼"- to ½" internal diameter Tygon tubing with negligible compliance.

Instantaneous flow rates were measured by using a transit-time ultrasound flowmeter (HT110 series, Transonic System, Ithaca, NY, USA).

Pressures were measured by pressure transducers (140 PC pressure sensor, Honeywell, NY, USA). Flow and pressure were sampled at 200Hz using a proper acquisition system DAQPad-6020E (National Instruments, Inc., Austin, TX, USA). Water at 22°C (density of $\rho = 1000$ kg/m^3 and viscosity of $\mu = 0.001$ Pa·s) was used in these experiments. All the tests were performed setting the Ikus Driving Unit at a heart rate of 130 bpm and systolic time of 35%.

TABLE I

Par.	*Value*	*Par.*	*Value*
R_{AO}	$4.00\left[\frac{mmHg \cdot min}{l}\right]$	L_{AO}	$3.0 \cdot 10^{-3}\left[\frac{mmHg \cdot s^2}{l}\right]$
R_{UB}	$0.65\left[\frac{mmHg \cdot min}{l}\right]$	C_{AO}	$3.0 \cdot 10^{-4}\left[\frac{l}{mmHg}\right]$
R_{LB}	$0.82\left[\frac{mmHg \cdot min}{l}\right]$	L_{UB}	$6.0 \cdot 10^{-4}\left[\frac{mmHg \cdot s^2}{l}\right]$
R_P	$5.00\left[\frac{mmHg \cdot min}{l}\right]$	C_{UB}	$1.6 \cdot 10^{-3}\left[\frac{l}{mmHg}\right]$
R_{IVC}	$0.50\left[\frac{mmHg \cdot min}{l}\right]$	L_{LB}	$1.8 \cdot 10^{-3}\left[\frac{mmHg \cdot s^2}{l}\right]$
R_{SVC}	$0.10\left[\frac{mmHg \cdot min}{l}\right]$	C_{LB}	$4.3 \cdot 10^{-3}\left[\frac{l}{mmHg}\right]$
L_P	$1.9 \cdot 10^{-3}\left[\frac{mmHg \cdot s^2}{l}\right]$	C_P	$5.3 \cdot 10^{-3}\left[\frac{l}{mmHg}\right]$

Parameters used in the electrical model of the BCPC physiological conditions, then replicated in the in-vitro test bench.

Physiological conditions were replicated and compared with catheterization data obtained from 20 children with Glenn circulation. BCPC circulation can fail for many reasons. Systolic dysfunction, diastolic dysfunction, elevated PVR, and a combination these "failing" Glenn physiology [17], were simulated.

III. Results

Measured pressure and flow values are compared directly to the catheterizations obtained from 20 patients (Table 2) aged 4 years old on average (BSA = 0.68 m^2). Signals were averaged on 30 seconds of contiguous cycles. Systolic and diastolic pressures were set in the physiological condition at 115 mmHg and -17.5 mmHg, respectively, to achieve an ejection fraction of 66%.

Setting the Glenn resistance, the resistance of the shunt, to "physiological" value of 1 wood unit (1 WU = 1 mmHg · min · l^{-1}) it was possible to achieve a mean flow rate equal to 1.32 ± 0.07 l/min, a mean aortic pressure (MAP) of 87 mmHg a pulmonary arterial pressure (PAP) of 10 mmHg and an atrial pressure (AP) of 4 mmHg.

The trans-gradient pressure (TGP) the difference between PAP and AP is 4 mmHg. All these values are very close to the in-vivo catheterizations, only the PAP (and consequently the TGP) in the in-vitro test was 1 mmHg higher than the pressure in the in-vivo conditions. Four different dysfunctions were replicated. To mimic the diastolic dysfunction, the diastolic pressure was increased from -17.5 mmHg to -12.5 mmHg, the systolic pressure was kept constant at 115 mmHg, and the aortic resistance was adjusted (decreased) to obtain the same flow rate of the physiological condition (1.32 l/min). In these conditions, the PAP remains constant while the MAP decreases to 75 mmHg. As expected with the diastolic dysfunction, the AP raise from 6 to 8.2 mmHg. Starting from the physiological condition, to take off the systolic dysfunction, only the diastolic pressure was increased from -17.5 mmHg to -10 mmHg. As expected, the flow rate and consequently, the MAP decrease to 0.95 l/min and 58 mmHg, respectively. Even in this case, the AP increase a lot from 6 to 9.8 mmHg while the PAP raises from 11 to 12 mmHg. To mimic the elevate PVR dysfunction, characterized by a very high cavo-pulmonary resistance that can lead to increased pulmonary artery pressures, the Glenn resistance was set to the pathological value of 4 WU. As anticipated, the cardiac output and the MAP does not chance from the physiological condition, while the PAP and the AP step up to 16 mmHg and 8.8 mmHg, respectively. In addition, the TGP increase from 6 mmHg to 8.8 mmHg. In the end, a complex mix of the previous failures was mimicked. Starting from physiological conditions, diastolic pressure and Glenn resistance were increased to 100 mmHg and 4 WU, respectively while the systolic pressure was reduced to 100 mmHg. Despite the decreasing of the cardiac output from 1.32 l/min to 1.1 l/min, the PAP increased from 10 mmHg to 16 mmHg, and the AP moved from 6 mmHg to 10 mmHg, the highest value ever achieved during these experiments.

TABLE II

		In-Vivo	*In-Vitro*				
Param.	*Units*	Physiological	Physiological	Diastolic dysfunction	Systolic dysfunction	Elevate PVR	Mixed type
Systolic Pressure	$[mmHg]$	[-]	115	115	115	115	100
Diastolic Pressure	$[mmHg]$	[-]	-17.5	-12.5	-10.0	-17.5	-10.0
Glenn Resistance	$\left[\frac{mmHg \cdot min}{l}\right]$	[-]	1	1	1	4	4
Flow rate	$[l/min]$	1.30	1.32	1.32	0.95	1.30	1.10
PAP	$[mmHg]$	11.3	10.0	11.0	12.0	16.0	16.2
AP	$[mmHg]$	6.2	7.0	8.2	9.8	8.8	10.0
TGP	$[mmHg]$	5.1	4.0	3.0	2.0	7.0	6.0
MAP	$[mmHg]$	70-90	87	75	58	86	70

Data obtained from catheterization and in-vitro tests. The catheterization data came from 20 children that were in stable Glenn circulatory conditions at the Newcastle Childhood Hospital (UK). Systolic and diastolic pressure were set by the Ikus while Glenn resistance was set in the test bench. Physiological condition, systolic dysfunction, diastolic dysfunction, elevated pulmonary vascular resistance (PVR), and a combination these "failing" Glenn physiology (Mixed type) were reproduced.

As expected, due to the decreasing of the cardiac output and having kept the aortic resistant constant, the MAP decreased from 87 mmHg to 70 mmHg. Table 2 resumes the variations of flow rate, PAP, AP, TGP and MAP both in in-vivo (physiological) and in-vitro (physiological or failure) conditions.

IV. Discussion

We believe we have developed a very detailed in-vitro model of the bidirectional cavo-pulmonary circulation amenable of adjustments due to changing pathophysiological conditions. The measured pressure and flow rate showed an excellent correlation with the catheterization data from 20 patients in a BCPC pre-TCPC. Four pathological BCPC circulations were well reproduced by changing one parameter at a time or all at once. Observation of the response of the "patient" by changing one parameter at a time or all at once is possible with this model, allowing us to understand how to establish the most suitable MCS. In all the pathological conditions mimicked, the AP increased. It is well known [17] that it is necessary to employ a MCS not only to restore the correct cardiac output but also to offload the atrium and reduce the AP, the PAP and consequently the TGP. The selection strategy for patients who benefit the most from the device continues to evolve. It remains controversial which type of MCS we should use, either VA-ECMO or VADs (with continuous or pulsatile flow, axial or centrifugal) and in which positions (atrial-arterial or ventricular-arterial cannulation). It has been proposed that the optimal mechanism for supporting univentricular patients depends on the aetiology of failure [17], for this reason, a tool capable of reproducing different mechanism of failures could be very useful to understand better how to treat these patients. In several clinical scenarios it remains controversial which type of MCS surgeons should use; using this new in-vitro test bench, it is possible to set patient-specific parameters to understand better how to treat this patient and which device is more appropriate for that pathology. In the experiments reported in this work, we have used the Berlin Heart Excor pulsatile pump as baseline native heart and ventricular assist device. The reason for this choice was mainly related to the size of patients whose cardiac catheterisation data were used as a reference. These children with single ventricle failure nowadays are only supported with Berlin Heart Excor being it the only available device for small size patients. However, the mock circulatory system can be easily connected to other ventricular assist devices like non-pulsatile pumps, either axial or centrifugal, leaving the Berlin Heart Excor as native heart as it allows easy adjustments to mimic the different types of failure and can allow reproducing the effects of the neurohormonal response (i.e. vasoconstriction due to low cardiac output etc.), by adjusting upper and lower body resistance. The proposed mock circulatory system can also be easily turned into a TCPC model by connecting the inferior vena cava draining the LB to the pulmonary artery system instead of the left atrium, or into the already mentioned and reproduced clinical scenarios or be connected to other different assist devices.

Acknowledgements

We would like to thanks Berlin Heart (Berlin Heart, GmbH, Wiesenweg 10, 12247 Berlin – Germany) for supplying all the Excor® VADs used and the Ikus Driving Unit.

References

[1] Freedom RM, Nykanen D, Benson LN. The physiology of the bidirectional cavopulmonary connection. Ann Thorac Surg. 1998;66(2):664-667. doi:10.1016/S0003-4975(98)00618-3.

[2] Kopf GS, Laks H, Stansel HC, Hellenbrand WE, Kleinman CS, Talner NS. Thirty-year follow-up of superior vena cava-pulmonary artery (Glenn) shunts. J Thorac Cardiovasc Surg. 1990;100(5):661-662.

[3] Reddy VM, McElhinney DB, Moore P, Haas GS, Hanley FL. Outcomes after bidirectional cavopulmonary shunt in infants less than 6 months old. J Am Coll Cardiol. 1997;29(6):1365-1370. doi:10.1016/S0735-1097(97)00068-5.

[4] Lamberti JJ, Spicer RL, Waldman JD, et al. The bidirectional cavopulmonary shunt. J Thorac Cardiovasc Surg. 1990;100(1):22-30.

[5] Hopkins RA, Armstrong BE, Serwer GA, Peterson RJ, Oldham HN. Physiological rationale for a bidirectional cavopulmonary shunt. A versatile complement to the Fontan principle. J Thorac Cardiovasc Surg. 1985;90(3):391-398.

[6] Bridges ND, Jonas R a, Mayer JE, Flanagan MF, Keane JF, Castaneda a R. Bidirectional cavopulmonary anastomosis as interim palliation for high-risk Fontan candidates. Early results. Circulation. 1990;82(5 Suppl):IV170-6.

[7] Mondésert B, Marcotte F, Mongeon FP, et al. Fontan circulation: Success or failure? Can J Cardiol. 2013;29(7):811-820. doi:10.1016/j.cjca.2012.12.009.

[8] Bagai A, O'Brien S, Al Lawati H, et al. Mentored simulation training improves procedural skills in cardiac catheterization: A randomized, controlled pilot study. Circ Cardiovasc Interv. 2012;5(5):672-679. doi:10.1161/CIRCINTERVENTIONS.112.970772.

[9] Dur O, Lara M, Arnold D, et al. Pulsatile in vitro simulation of the pediatric univentricular circulation for evaluation of cardiopulmonary assist scenarios. Artif Organs. 2009;33(11):967-976. doi:10.1111/j.1525-1594.2009.00951.x.

[10] Di Molfetta A, Amodeo A, Fresiello L, et al. Simulation of Ventricular, Cavo-Pulmonary, and Biventricular Ventricular Assist Devices in Failing Fontan. Artif Organs. 2015;39(7):550-558. doi:10.1111/aor.12434.

[11] Pantalos GM, Ionan C, Koenig SC, et al. Expanded pediatric cardiovascular simulator for research and training. ASAIO J. 2010;56(1):67-72. doi:10.1097/MAT.0b013e3181c838ae.

[12] Zhou J, Esmaily-Moghadam M, Conover TA, Hsia TY, Marsden AL, Figliola RS. In Vitro Assessment of the Assisted Bidirectional Glenn Procedure for Stage One Single Ventricle Repair. Cardiovasc Eng Technol. 2015;6(3):256-267. doi:10.1007/s13239-015-0232-z.

[13] Hussain A, Arfi AM, Hussamuddin M, et al. Comparative Outcome of Bidirectional Glenn Shunt in Patients With Pulmonary Vascular Resistance ≥ 3.5 Woods Units Versus < 3.5 Woods Units. Am J Cardiol. 2008;102(7):907-912. doi:10.1016/j.amjcard.2008.04.063.

[14] Baretta A, Corsini C, Yang W, et al. Virtual Surgeries in Patients with Congenital Heart Disease: A Multi-scale Modelling Test Case. Philos Trans A Math Phys Eng Sci. 2011;369(1954):4316-4330. doi:10.1098/rsta.2011.0130.

[15] Vukicevic M, Chiulli JA, Conover T, et al. Mock circulatory system of the Fontan circulation to study respiration effects on venous flow behavior. ASAIO J. 2013;100(2):253-260. doi:10.1016/j.pestbp.2011.02.012.Investigations.

[16] Kung EO, Taylor CA. Development of a Physical Windkessel Module to Re-Create In Vivo Vascular Flow Impedance for In Vitro Experiments. Cardiovasc Eng Technol. 2011;2(1):2-14. doi:10.1007/s13239-010-0030-6.

[17] Horne D, Conway J, Rebeyka IM, Buchholz H. Mechanical Circulatory Support in Univentricular Hearts: Current Management. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2015;18(1):17-24. doi:10.1053/j.pcsu.2015.02.002.