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Intraoperative transit-time flow measurement of caval veins before and after bidirectional cavopulmonary anastomosis

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Abstract

Background: Haemodynamic changes in caval venous flow distribution occurring during bidirectional cavopulmonary anastomosis operation are still largely unknown. Methods: Transit time flow measurements were performed in 15 cavopulmonary anastomosis operations. Superior and inferior caval vein flows were measured before and after the cavopulmonary anastomosis. Ratio of superior caval vein to overall caval veins flow was calculated. Results: Mean superior caval vein flow ratio before cavopulmonary anastomosis was higher than previously reported for healthy children. Superior caval vein flow ratio decreased in 14/15 patients after cavopulmonary anastomosis: mean 0.63 ± 0.12 before versus 0.43 ± 0.14 after. No linear correlation between intraoperative superior caval vein pressure and superior caval vein flow after cavopulmonary anastomosis was found. Neither Nakata index nor pulmonary vascular resistance measured at preoperative cardiac catheterisation correlated with intraoperative flows. None of patients died or required a take down. Conclusions: The higher mean superior caval vein flow ratio before cavopulmonary anastomosis compared to healthy children suggests flow redistribution in univentricular physiology to protect brain and neurodevelopment. The decrease of superior caval vein flow ratio after cavopulmonary anastomosis may reflect the flow redistribution related to trans-pulmonary gradient. The lack of correlation between superior caval vein pressure and superior caval vein flow could be explained by limited sample size and multifactorial determinants of caval veins flow, although pressure remain essential. Larger sample of measurements are needed to find flow range potentially predictive for clinical failure. To authors' knowledge, this is the first intraoperative flow measurement of both caval veins during cavopulmonary operations.

In 1958, William Glenn performed the first clinical shunt operation between the superior caval vein and the right pulmonary artery in a patient and in 1965 the clinical results of the first 38 patients were published. ^{1–2} At that time, the indication for a cavopulmonary anastomosis was any condition in which there was intra-cardiac mixing and reduced blood flow to the lungs. Nowadays, the bidirectional cavopulmonary anastomosis, also known as "Glenn operation", represents a standard surgical step in patients with single ventricle physiology. The changes in caval venous flow distribution, if any, occurring in the bidirectional cavopulmonary anastomosis operation are still largely unknown. The aim of this study was to perform direct intraoperative measurements of superior and inferior caval vein flow before and after the cavopulmonary anastomosis in order to analyse the physiologic and haemodynamic changes occurring during the operation and the consequent changes in caval flow distribution.

Material and methods

Patient selection

Between 2016 and 2023, we prospectively studied 15 patients with single ventricle physiology who underwent a cavopulmonary anastomosis operation. All patients underwent an initial palliative intervention: 7 aorto-pulmonary shunt, 4 Norwood stage I and 2 Norwood-like operations, 1 pulmonary artery banding, and 1 ductal stenting.

Although the Institutional Review Board of University Medical Center Groningen waived the need for an informed consent (Medical Ethical Committee University Medical Center Groningen number 2015.532), the parents of all participating patients were informed about the intraoperative flow measurement, and none expressed any objections.

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Methods

All except one patient underwent a preoperative cardiac catheterisation with measurement of indexed pulmonary vascular resistance (Wood unit/m²). One patient did not undergo a preoperative cardiac catheterisation because based on echocardiography and CT scan there were no clinical concern for elevated pulmonary vascular resistance and anatomical lesions which could have required catheterisation interventions prior to the cavopulmonary operation.³

Left pulmonary artery and right pulmonary artery diameter were calculated by means of cardiac catheterisation angiography in 13 patients and by means of cardiac computerised tomography in 2 patients. Nakata index was calculated as $\frac{\text{left pulmonary artery area } (\text{mm}^2) + \text{right pulmonary artery area } (\text{mm}^2)}{\text{BSA } (\text{m}^2)}.4$

Caval veins flows were measured by ultrasound transit time flow measurement using Medistim Vascular probes and Medistim VeriQTM system (Medistim ASA, Oslo – Norway). The flow was measured in ml/min. The probe diameter was selected in order to ensure optimal acoustical contact and was positioned around the caval veins trying to avoid any vessel distortion or narrowing. Acoustic coupling index was used to assess the quality and reliability of the measurements, and only measurements with an acoustic coupling index above 50% were included.

Superior and inferior caval vein flows were measured before and after the cavo-pulmonary shunt. The first measurement was performed before initiation of cardio-pulmonary bypass and before routine ligation of the azygos vein, upstream of the azygos vein. The second measurement was performed after weaning from cardio-pulmonary bypass and before the administration of protamine, in order to avoid any possible change in pulmonary vascular resistance caused by protamine. In one patient with bilateral superior caval veins, the total superior caval vein flow was considered to be as the sum of the flows measured in both superior caval veins.

The indexed caval veins flow was calculated using BSA as dominator and measured in ml/min/m². BSA was calculated using Haycock's formula.

Superior caval vein flow ratio was calculated as follows: superior caval vein flow

superior caval vein flow + inferior caval vein flow

The total venous return was calculated as: indexed superior caval vein flow + indexed inferior caval vein flow, corresponded to the systemic flow.

In all patients superior caval vein pressure was measured by means of a jugular venous catheter.

Postoperative arterial saturation, under normoxic conditions, was measured by pulse oximetry at the time of discharge from the hospital.

In Vitro transit time flow measurements were performed to verify the accuracy and reliability of the Medistim Vascular probes, and the results are described in the supplementary material.

Surgical technique bidirectional cavopulmonary operation

All operations were performed through a median sternotomy; cardio-pulmonary bypass was established with double venous cannulation and normothermia was maintained. An end-to-side anastomosis between superior caval vein and right pulmonary artery was performed. In one patient with bilateral superior caval veins, the bilateral bidirectional cavo-pulmonary anastomosis was performed with the "V-shape technique": the bilateral caval anastomoses were constructed adjacent to each other on

the midline of the pulmonary artery bifurcation. If aortic cross clamping was needed, a single-dose antegrade Custodiol® HTK cardioplegia was administrated. Aortic cross clamping was needed for additional cardiac interventions in 2 patients: one atrioseptectomy and one atrioseptectomy with a repair of left pulmonary artery stenosis. None of the included patients had a known source of additional pulmonary blood flow after the operation: all pre-existent aorto-pulmonary shunts were closed during the operation and, in the presence of persistent antegrade pulmonary blood flow, the pulmonary valve was closed as well.

All operations were performed using standard mechanical ventilation settings: tidal volume 6–8 ml/kg and when necessary, adjusted to reduce trans-pulmonary pressure and ventilation to maintain normocapnia: during measurements partial pressure of carbon dioxide range was 30–45 mmHg (mean pCO $_2$ before cavo-pulmonary anastomosis 40 mmHg and 41 mmHg after). Inspired oxygen concentrations were adjusted to obtain percutaneous oxygen saturation levels of >75-80% after cavo-pulmonary anastomosis. Even in cases when the superior caval vein flow was markedly reduced, no attempt was made to achieve some degree of hypercapnia to decrease cerebral vascular resistance and increase cerebral, superior caval vein, and pulmonary blood flow.

After initiation of cardio-pulmonary bypass haemoglobin level was maintained above 9 g/dL.

Most patients received a low to medium dose of milrinone (0.35–0.5 μ g/kg/min) before discontinuation of cardio-pulmonary bypass, if necessary supplemented with low-dose noradrenaline or dopamine to achieve stable hemodynamics. None of the patients required the administration of nitric oxide.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics 23 (IBM Corporation, New York, USA). Values are reported as mean \pm standard deviation.

Pearson's correlation coefficient was used to analyse the following correlations:

- indexed superior caval vein flow before and after cavopulmonary anastomosis.
- indexed inferior caval vein flow before and after cavopulmonary anastomosis.
- total venous return before and after cavopulmonary anastomosis.
- indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary anastomosis with Nakata index.
- indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary anastomosis with pulmonary vascular resistance measured at preoperative cardiac catheterisation.
- indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary anastomosis with intraoperative superior caval vein pressure.
- indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary anastomosis with postoperative arterial saturation.

A p-value less than 0.05 was used to indicate statistical significance.

Table 1. Baseline and preoperative patient characteristics

				At time of BCPS operation		
Patient	Gender	Diagnosis	Previous palliative intervention(s)	Age (months)	Weight (kg)	BSA (m²)
1	F	Tricuspid atresia, hypoplastic RV, pulmonary atresia	Central aorto-pulmonary shunt, atrioseptectomy	6.68	6	0.33
2	М	Tricuspid atresia, hypoplastic RV, VSD, bilateral superior caval veins	1 st :pulmonary artery banding	21.64	11	0.50
			2 nd :debanding and central aorto-pulmonary shunt			
3	М	HLHS	Norwood I	5.79	10	0.46
4	F	HLHS	Norwood I	3.91	6	0.32
5	F	Tricuspid atresia, TGA, VSD, coarctation, hypoplastic arch	DKS, coarctectomy, central aorto-pulmonary shunt, atrioseptectomie	4.11	6	0.33
6	F	Mitral atresia, double discordance	DKS, central aorto-pulmonary shunt, atrioseptectomy	5.49	7	0.36
7	F	Tricuspid atresia	Central aorto-pulmonary shunt	10.59	7	0.38
8	М	HLHS	Norwood I	11.02	7.7	0.39
9	М	Tricuspid atresia	Central aorto-pulmonary shunt	9.54	7.7	0.39
10	М	DILV, TGA, hypoplastic arch	Norwood I	4.77	6.8	0.35
11	М	Unbalanced AVSD, hypoplastic RV	Central aorto-pulmonary shunt	7.14	7.8	0.39
12	F	Pulmonary atresia	Ductus stenting	5.36	5.5	0.31
13	F	Pulmonary atresia, hypoplastic RV	Central aorto-pulmonary shunt	6.58	7	0.36

AVSD = atrioventricular septal defect; BCPS = bidirectional cavo-pulmonary shunt; BSA = body surface area; DILV = double-inlet left ventricle; DKS = Damus-Kaye-Stansel; F = female; HLHS = hypoplastic left heart syndrome; M = male; RV = right ventricle; TGA = transposition great arteries; VSD = ventricle septal defect.

Results

Baseline patients' characteristics are shown in Table 1. The mean age at operation was 8 ± 4 months, and mean BSA was $0.37\pm0.05~\text{m}^2$.

Table 2 reported the parameters used to perform Pearson's correlation coefficient: pulmonary vascular resistance measured at preoperative cardiac catheterisation, Nakata index, intraoperative superior caval vein pressure, indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary anastomosis, postoperative arterial saturation. Patient 13 with Nakata index $90 \text{ mm}^2/\text{m}^2$ underwent a left pulmonary artery plasty. Patient 14 did not undergo a preoperative cardiac catheterisation. Mean postoperative arterial saturation at discharge was $77 \pm 7\%$ (range 68-89%).

Figure 1 shows the change of intraoperative total venous return, caval veins flows and superior caval vein flow ratio per patient before and after cavopulmonary anastomosis.

After cavopulmonary anastomosis, the total venous return increased in 11 patients, remained the same in 1 patient and decreased in 3 patients (Figure 1a).

Indexed superior caval vein flow decreased in 8 patients, remained the same in 1 patient and increased in 6 (Figure 4b). Indexed inferior caval vein flow increased in 14 patients and remained the same in 1 patient (Figure 4c).

Mean indexed superior caval vein flow decreased after cavopulmonary anastomosis ($1202 \pm 553 \text{ ml/min/m}^2$ before versus $1025 \pm 485 \text{ ml/min/m}^2$ after), whilst mean indexed inferior caval vein flow increased after the cavopulmonary anastomosis ($757 \pm 564 \text{ ml/min/m}^2$ before versus $1365 \pm 663 \text{ ml/min/m}^2$ after).

The superior caval vein flow ratio after the cavopulmonary anastomosis decreased in 14 patients, in one patient (patient 5 on Figure 4d) an increase of 5% of superior caval vein flow ratio was observed.

Mean superior caval vein flow ratio decreased after the cavopulmonary anastomosis: 0.63 ± 0.12 before, compared to 0.43 ± 0.14 after.

There was a positive trend towards linear correlation between indexed superior caval vein flow before and after cavopulmonary anastomosis: Pearson correlation coefficient r=0.507, p=0.054. There was a positive linear correlation between indexed inferior caval vein before and after cavopulmonary anastomosis and between total venous return before and after cavopulmonary anastomosis: Pearson correlation coefficient r=0.661, p=0.007 and r=0.622, p=0.013, respectively.

No linear correlation was found between Nakata index and either indexed superior caval vein flow or superior caval vein flow ratio after the cavopulmonary anastomosis: Pearson correlation coefficient $r=0.234,\,p=0.401$ and $r=0.060,\,p=0.831,$ respectively.

No linear correlation was found between pulmonary vascular resistance measured at preoperative cardiac catheterisation and either indexed superior caval vein flow and superior caval vein flow ratio after the cavopulmonary anastomosis: Pearson correlation coefficient r=-0.085, p=0.772 and r=0.114, p=0.698, respectively.

Neither indexed superior caval vein flow nor superior caval vein flow ratio after the cavopulmonary anastomosis correlated with superior caval vein pressure, measured intraoperatively: Pearson 4 S. C. Arrigoni et al.

Table 2. Pulmonary vascular resistance at preoperative cardiac catheterisation, Nakata index, intraoperative superior caval vein pressure, indexed superior caval vein flow and superior caval vein flow ratio after cavopulmonary operation, postoperative arterial saturation

	Preope	rative	Intraoperative after BCPS		Postoperative at discharge		
Patient	Indexed PVR (Wood unit/m²)	Nakata index (mm²/m²)	SCV pressure (mmHg)	Indexed SCV flow (ml/min/m²)	SCV flow ratio	Arterial saturation (%)	
1	1.61	265	16	942	0.35	85	
2	2.80	282	10	1534	0.68	80	
3	2.40	146	15	671	0.35	82	
4	2.20	128	15	613	0.30	75	
5	1.15	108	17	1195	0.63	75	
6	0.95	254	15	443	0.32	80	
7	1.43	491	19	1037	0.51	87	
8	2.36	327	22	657	0.40	83	
9	0.71	317	18	2242	0.45	80	
10	1.55	161	14	1054	0.31	68	
11	0.54	413	14	546	0.31	77	
12	1.06	269	13	1048	0.62	73	
13	0.99	90	17	730	0.39	89	
14		389	16	1684	0.40	85	
15	1.20	108	16	976	0.46	78	

BCPS = bidirectional cavo-pulmonary shunt; PVR = pulmonary vascular resistance; SCV = superior caval vein.

correlation coefficient r = -0.039, p = 0.889 and r = -0.207, p = 0.458, respectively.

Neither indexed superior caval vein flow nor superior caval vein flow ratio after the cavopulmonary anastomosis correlated with postoperative arterial saturation at discharge: Pearson correlation coefficient r=0.019, p=0.946 and r=-0.054, p=0.849, respectively.

Discussion

Transit time flow measurement is widely used to assess patency of coronary artery bypass grafting^{5–7} and is gaining applications in transplant surgery.⁸ To authors' knowledge, this is the first report of intraoperative transit time flow measurement of both caval veins which is focused on the flow changes that occur during a cavopulmonary operation.

The transit time flow measurement of superior and inferior caval veins was technically feasible and safe, which means that we could manage accurate flow measurements without compromising the haemodynamic stability of the patients.

The wide range of indexed superior and inferior caval veins and total venous return could be explained by the variability of anatomical parameters among patients. In fact, the cross-sectional area of caval veins varied among our patients, confirmed by the different transit time flow measurement probe diameters required to perform the measurements. Moreover, vein walls possess a layered configuration consisting of a thin wall and elastic media, smooth muscle, and a thick collagenous adventitia: the development, growth and ratio of these layers can vary among patients, influencing the vascular function and compliance of caval veins. 9–10 Furthermore, caval veins flow could have been influenced by intraoperative mechanical ventilation and

medication. The positive end-expiratory pressure of mechanical ventilation could increase the abdominal pressure facilitating inferior caval vein collapse and, similarly, tidal ventilation could increase pleural pressure facilitating partial collapse of superior caval vein. The standard settings of mechanical ventilation did not exclude variations among patients and individual adjustments during the operation.

In addition, the cardiac, pulmonary, and peripheral vascular circulation could have been influenced by the medical management under general anaesthesia. In fact, in 10 patients, milrinone was administrated upon weaning from cardio-pulmonary bypass because of its combined effect of decreasing pulmonary vascular resistance and cardiac positive inotropic effect (noradrenaline was administrated in 5 patients and dopamine in 2). The different combination of intravenous medications could have contributed to modulate the venous flow distribution.

Our results as far as superior caval vein flow concerns, seem quite different from those previously reported by Kotani and colleagues, in which intraoperative measurement of superior caval vein flow was performed during cavopulmonary operations.¹¹ In fact, mean indexed superior caval vein flow either before or after cavopulmonary anastomosis of our study are lower compared to the flows registered by Kotani and colleagues (before cardiopulmonary anastomosis 1202 ± 553 ml/min/m² of our study compared to 1630 ± 550 ml/min/m² of Kotani's and after cardiopulmonary anastomosis $1025 \pm 485 \text{ ml/min/m}^2$ of our study compared to $1990 \pm 570 \text{ ml/min/m}^2$ of Kotani's). Furthermore, a significant increase in mean superior caval vein flow after cavopulmonary anastomosis is reported in Kotani's study whilst in our study mean indexed superior caval vein flow decreased after cavopulmonary anastomosis. These differences could be explained by the different standard setting established during the

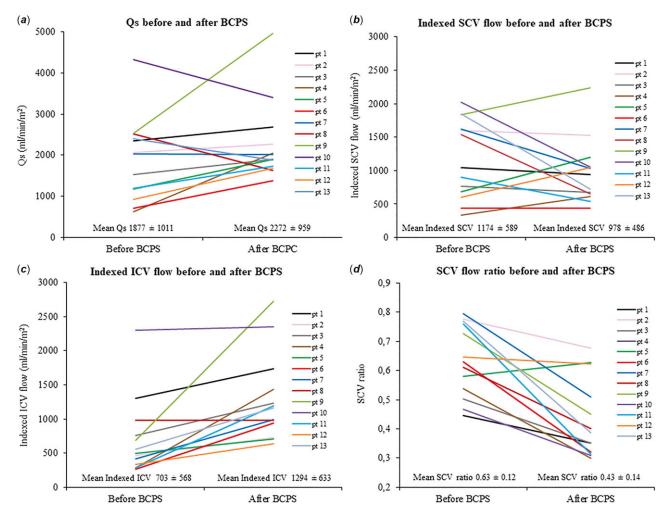


Figure 1. Transit time flow measurement of caval veins flows, total venous return and superior caval vein flow flow ratio measured per patient before and after cavopulmonary anastomosis. 1a. Total venous return measured in each patient before and after cavopulmonary anastomosis. 1b. Indexed superior caval vein flow measured in each patient before and after cavopulmonary anastomosis. 1c. Indexed inferior caval vein flow measured in each patient before and after cavopulmonary anastomosis. 1d. Superior caval vein flow ratio measured in each patient before and after cavopulmonary anastomosis. BCPS = bidirectional cavopulmonary shunt; ICV = inferior caval vein; pt = patient; Qs = total venous return; SCV = superior caval vein.

measurements. In fact, in Kotani's study both partial pCO₂ and haemoglobin level were maintained in ranges higher than our study (pCO₂ 45–55 mmHg and haemoglobin > 14 g/dL by Kotani's compared to pCO₂ 30–45 mmHg and haemoglobin > 9 g/dL in our study). Moreover, our patients received a low to medium dose of milrinone (0.3–0.5 μ g/kg/min) compared to a higher dose (0.66–0.99 μ g/kg/min) administrated in Kotani's patients. Higher pCO₂, haemoglobin level, and milrinone dose contribute to facilitate pulmonary blood flow. Our policy does not contemplate to increase superior caval vein and pulmonary blood flow by means of hypercapnia and anaesthesia adjustments: we attempt to create an "untouched" physiological setting with the minimal artificial gain.

Low superior caval vein flow before cardiopulmonary anastomosis has been previously associated to cardiopulmonary operation failure: 2 patients who died or required a take down in Kotani's study had a superior caval vein flow < 1000 ml/min/m² and all patients included in a cardiac magnetic resonance study who experienced a failure had a superior caval vein flow < 1600 ml/min/m². 11,12 No one of our patients died or required a take down, although 6 patients had a superior caval vein flow < 1000 ml/min/m² and 9 patients < 1600 ml/min/m². Therefore, our study could not confirm this association.

The mean superior caval vein flow ratio before cavopulmonary anastomosis of our study (0.63 ± 0.12) seems higher than the mean ratio of healthy children of comparable age, although measured with a different technology and without usage of anaesthesia. In fact, echocardiographic studies of 145 healthy children showed a range of superior caval vein flow ratio from 0.49 (in newborn infants) up to 0.55 (at the age of 2.5 years). This difference may confirm the role of the cerebral vascular autoregulation which could alter the distribution of cardiac output between upper and lower body in order to preserve brain flow. In fact, in univentricular physiology because of intra-cardiac mixing and chronic hypoxaemia lower cerebrovascular resistance may be protective for neurodevelopment, as found in fetal studies. $^{14-15}$

The mean superior caval vein flow ratio after cavopulmonary anastomosis of our study (0.43 ± 0.14) is comparable with the range found by a previous cardiac magnetic resonance study performed in children at mean interval of 7.8 months from the cavopulmonary anastomosis (0.46 ± 0.08) . However, cardiac magnetic resonances performed later after cardiopulmonary operation, at mean interval of 28.3 months from the cavopulmonary anastomosis, showed a ratio higher than expected (0.55 ± 0.05) suggesting a postoperative time-dependent evolution

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of this ratio which does not decrease with age, as in healthy children. ¹³ The redistribution of flow between upper and lower body by means of vascular autoregulation could again be responsible of the increased ratio later after cavopulmonary operation. A "two-stages" evolution of caval veins flow distribution after cavopulmonary operation can be hypothesised: an early stage with decrease of superior caval vein flow ratio as direct effect of the trans-pulmonary gradient and a late stage with remodelling of vascular resistance, redistribution of flow and consequent increase of superior caval vein flow ratio.

The decrease of superior caval vein flow ratio direct after cavopulmonary anastomosis reported in our measurements (14/15 patients of our study) could be explained by the intrinsic physiology of the cavopulmonary connection. Before cavopulmonary anastomosis superior and inferior caval vein flows depend on the same systemic venous pressure among other parameters, whilst after, pulmonary artery resistance is added to total upper body outflow resistance: the lower systemic venous resistance facilitates inferior caval vein flow whilst the higher pulmonary artery resistance influences superior caval vein flow. The difference pressure to be faced by lower and upper body after cavopulmonary anastomosis, the so-called trans-pulmonary gradient contributes to determine superior caval vein flow ratio.

However, there was no linear correlation between pulmonary vascular resistance measured at preoperative cardiac catheterisation or superior caval vein pressure measured intraoperatively and indexed superior caval vein flow or flow ratio after cavopulmonary anastomosis. This lack of correlation could be explained by the combination of variables that influence blood flow, although pressure and vascular resistance remain essential determinants.¹⁷ Haemodilution during cardio-pulmonary bypass by reducing blood viscosity or the variable geometry of the cavopulmonary connection could influence caval veins flow, the pressure being equal. We could speculate that in a later postoperative phase the acute changes of some variables occurring during the operation (for instance, the hemodilution of cardiopulmonary bypass or the influence of general anaesthesia), could evolve towards a more physiological equilibrium, theoretically more comparable with the preoperative setting. In this more balanced setting, the acute change of intraoperative variables fades and could be overruled by the factors measured prior to the operation. This assumption could imply a potential change in the correlation between the preoperative variables and the intraoperative measurements. Moreover, the limited sample size of the study could have potentially affected the statistical power of the correlation.

No linear correlation was found between Nakata index and either indexed superior caval vein flow or flow ratio after cavopulmonary anastomosis. Our findings supported the belief that pulmonary artery sizes should not be considered an absolute limiting factor in the decision on treatment of functionally single ventricle patients. ^{18–19}

A correlation between the amount of superior caval vein flow after cavopulmonary anastomosis and the postoperative arterial saturation could be hypothesised. However, in our and previous studies, no linear correlation has been found. ¹² There are many factors in univentricular physiology such as collateral circulation of unknown magnitude or micro-vascular alteration of the pulmonary vascular bed which could vary among patients and concur determining arterial saturation.

The main limitation of this study is its single centre nature and the small cohort of patients. Although we are aware that this is a preliminary study, our findings could promote the application of flow measurement technology, improving the knowledge of the physiological change occurring during cavopulmonary operation. Because none of our patients died or required a take down of the cavopulmonary anastomosis, we could not identify range of flows potentially predictive for failure.

To conclude: intraoperative transit time flow measurement of caval veins during cavopulmonary operation was technically feasible and safe. The mean superior caval vein flow ratio before cavopulmonary anastomosis seemed higher compared to healthy children, suggesting a redistribution of flow in univentricular physiology to protect brain and neurodevelopment. The decrease of superior caval vein flow ratio registered after cavopulmonary anastomosis could reflect the physiological flow redistribution related to the trans-pulmonary gradient. The lack of linear correlation between superior caval vein pressure and indexed superior caval vein flow could be explained by the interaction of multifactorial determinants of caval veins flow, although pressure plays an essential role. Further measurements are needed to estimate caval veins flows and flow ratio potentially predictive for failure, therefore identifying patients at risk for take down.

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