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Analysis of post-operative systemic to pulmonary artery shunt failure

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Abbreviations: MBTS: Modified Blalock-Taussig shunt; RV-PA: Right ventricle to pulmonary artery; UFH: Unfractionated heparin; PTFE: Polytetrafluoroethylene; PDA: Patent ductus arteriosus; AT: Antithrombin; RPA: Right pulmonary artery; LAP: Left pulmonary artery; MPA: Main pulmonary artery; PAB: Pulmonary artery band.

Abstract

Background: Systemic to pulmonary artery shunts are utilized in the palliation of children with congenital heart disease and limited or ductal dependent pulmonary blood flow.

Methods: This case-control series matched all children at our institution between 2009 and 2015 who had an acute systemic-to-pulmonary artery shunt complication to subjects without acute shunt complication. Subjects were matched according to weight (within 10%), shunt type and size, and use of cardiopulmonary bypass. Nine variables, identified *a priori*, were compared to determine factors associated with acute shunt failure.

Results: Seventeen subjects with shunt failure were identified during the study period. Two infants were excluded because their shunts failed in the operating room prior to sternal closure. There were 10 right modified Blalock-Taussig shunts and five central shunts in each cohort. Shunt size was either 3.5 or 4.0 mm. Median (1st quartile-3rd quartile) age at time of surgery was 15 days (10-45) in the shunt complication cohort. Pulmonary artery size was the only factor that was statistically significant between the cohort with the acute shunt complication and the cohort without [median (1st quartile-3rd quartile) 3.70 mm (3.25-4.4) vs. 4.50 mm (4.00-5.10); p=0.014].

Conclusion: The impact of acute shunt complication on morbidity and mortality remains substantial. In this study, smaller pulmonary artery size was associated with increased risk of acute shunt failure. Further studies with sufficient power are required to determine additional modifiable risk factors.

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Introduction

Systemic to pulmonary artery shunts are an important procedure in the palliation of children with congenital heart disease and limited or ductal dependent pulmonary blood flow. Acute shunt complications, typically acute thrombosis, increase mortality in this fragile patient population. Early failure (defined as the first 30 days post shunt placement and sternal closure) of a systemic to pulmonary shunt is likely multi-factorial, but modifiable risk factors have not been clearly identified. The purpose of this case control series was to identify risk factors for acute shunt failure in children receiving a systemic to pulmonary artery shunt.

Patients and methods

This case control series matched patients who had an early shunt complication at Stollery Children's Hospital, Edmonton, Canada between 2009 and 2015 with patients without acute shunt complication. A systemic to pulmonary artery shunt was defined as a Modified Blalock-Taussig Shunt (MBTS), classic Blalock-Taussig shunt or a central shunt. Patients with a right ventricle to pulmonary artery (RV-PA) shunt were excluded as well as patients who had an intra-operative shunt complication that was successfully revised prior to sternal closure. Acute shunt complication was defined as a clinical presentation of acute hypoxemia unresponsive to increasing FiO2 along with clinical suspicion for shunt failure such as change in shunt murmur as well as echocardiographic evidence of poor shunt flow or angiographic evidence of shunt narrowing or occlusion, within 30 days of shunt placement and sternal closure. Cohorts were matched according to patient weight (within 10%), shunt type and size, and use of cardiopulmonary bypass. Cases and controls were identified through review of the surgical and Kid Clot (pediatric thrombosis team) databases. Our local institutional health research ethics board approved this study and waiver of informed consent.

Four surgeons were active during the study period. Unfractionated heparin (UFH) was bolused in the operating room (dose varied by surgeon) prior to occluding the vessels to create the shunt. The type and size of shunt placed, as well as ligation of the ductus arteriosus at the time of shunt placement was at the discretion of the operating surgeon. All shunts were performed with Gore-Tex expanded Polytetrafluoroethylene (PTFE) grafts (W.L. Gore & Assoc., Flagstaff, AZ).

We obtained information regarding the pre-, intra-, and post-operative course and morbidity and mortality through review of the hospital medical record, anesthesia record as well as operative and echocardiogram reports. The mechanism of shunt malfunction was ascertained via review of echocardiograms, cardiac catheterization and operative reports and classified as thrombosis or mechanical distortion of shunt or pulmonary arteries.

Given the small sample size, only a few clinically important variables were selected to analyze, in order to minimize the risk of finding significant results by chance. Nine variables were identified *a priori* based on review of the existing literature and our hypothesis that anticoagulation management may influence shunt failure,and compared between the two cohorts. These included:1) the presence of a non-cardiac congenital anomaly [1-3], 2) diameter of target pulmonary artery (measured by pre-operative transthoracic echocardiogram, diagnostic catheterization or cardiac MRI) [4,5], 3) patent ductus arteriosus (PDA) ligation at the time of shunt placement [6,7], 4) total UFH bolus in the operating room, 5) presence of alternative source of pulmonary blood flow post-operatively [7], 6) first post-operative antithrombin (AT) level, 7) time from post-operative intensive care admission to therapeutic anticoagulation (defined as the time of PICU admission to time to anti-factor Xa level ≥ 0.35 U/ml), 8) presence of post-operative bleeding (defined as drop in hemoglobin > 20g/L in first 24 hrs) [7] and 9) presence of a post-operative infection (defined as positive blood culture or sternal wound infection) [2,8].

During the time period of this study, UFH infusions were initiated at age-appropriate doses (10-28U/kg/hr for children less than one year of age) and titrated to therapeutic anti-factor Xa levels (0.35 – 0.7U/mL) [9] once post-operative bleeding was controlled. Patients with a shunt ≤ 3.5mm are discharged on low molecular weight heparin until their next staged palliation while patients with a shunt >3.5mm are treated with ASA (3-5mg/kg/day) once feeding until their next staged surgery.

Descriptive statistics were expressed as median (1st quartile - 3rd quartile) for continuous variables, and count (percentage) for categorical variables. The distributions of continuous variables were compared between the cohorts with and without acute shunt complications using the Mann-Whitney U tests, while the proportions of the categorical variables were compared using the Fisher's exact test or chi-square test. All data were analyzed using IBM SPSS Statistics Ver. 24 (IBM Corp.).

Results

During the study period, our institution performed 121 systemic to pulmonary artery shunts excluding RV-PA shunts. Seventeen cases of acute shunt complication were identified in the study period; two patients were excluded because their complication occurred exclusively intra-operatively, prior to sternal closure, and were successfully revised (15/121; 12.4%). Median (1st quartile - 3rd quartile) age and weight of the 15 subjects at the time of surgery was 15 days (10-45) and 3.4kg (3.0-3.5). Cardiac diagnoses, type and size of shunt placed, and outcomes of the cohort with acute shunt complication are shown in Table 1. The mechanism of shunt failure was thrombosis (confirmed by echocardiography, angiography or intraoperative findings) in 14 subjects (93%) and one subject had distortion of the right pulmonary artery and distal shunt (7%). Four subjects had multiple shunt complications including three who had an intra-operative shunt complication requiring shunt revision and additional UFH boluses in the OR as well as shunt failure after sternal closure. Subjects in the shunt complication group were older at the time of shunt placement than their weight matched cohort (p=0.037). Of the nine variables compared, smaller diameter of the pulmonary artery receiving the distal anastomosis was significantly associated (p=0.014) with shunt complication (Table 2). The target pulmonary artery was the right pulmonary artery (RPA) in 73% of patients, left pulmonary artery (LPA) in 7%, and main pulmonary artery (MPA) in 20%.

Comments

This series reports a 12.4% incidence of post operative shunt failure (11.5% incidence of shunt re-intervention) within 30 days and demonstrates that smaller pulmonary artery diameter, a non-modifiable risk factor, is significantly associated with shunt failure. These results are consistent with other reports that smaller pulmonary artery size is associated with post-operative shunt complication [4,5]. However, unlike previous studies, the

case-control design controls for patient weight at time of surgery, thereby confirming that pulmonary artery size is a significant risk factor independent of patient size. Although this risk factor is not modifiable, it does provide insight into which patients may be more likely to develop thrombotic complications. Whether patch augmentation of the pulmonary artery at the time of shunt placement mitigates this risk factor is unknown.

In addition, there was a statistically significant age difference between the two cohorts, with the shunt complication group being older at the time of shunt placement. This is counterintuitive as younger subjects with higher pulmonary vascular resistance should theoretically be at higher risk of low flow states across the shunt. This statistically significant finding is likely secondary to three complex patients who had their shunt deferred as a result of prematurity or failure of their original palliation. Specific within this cohort, subject 6 was born at 34 weeks gestation and was prostaglandin dependent until he had his shunt placed at 83 days of age (uncorrected gestational age). Subject 14 had hypoplastic left heart syndrome and was initially palliated with a Norwood procedure and 5mm Sano conduit; she presented with cyanosis at ten weeks of age and had a 3.5mm right MTBS at 78 days of age. Subject 4 was initially palliated with a pulmonary artery band (PAB) and total anomalous venous return repair. He was heterozygous for Factor V Leiden. His PAB was later taken down and his pulmonary arteries plicated, but he remained hypoxemic and was not a candidate for Glenn palliation as he had thrombosed his internal jugular and subclavian veins bilaterally. At 617 days, he went for a central shunt that acutely thrombosed his first post-operative night and was replaced with the same type and size of shunt. He again developed acute hypoxemia following shunt replacement and had a cardiac arrest.

The heterogeneous population of patients undergoing systemic to pulmonary artery shunt procedures, along with relatively small case numbers, makes it difficult to determine optimal management of these patients. The published incidence of systemic to pulmonary artery shunt occlusion varies from 6-17% [2,5,9]. The overall mortality of systemic to pulmonary shunt procedures is approximately 14% prior to next stage of repair, with shunt thrombosis being the leading cause of interim death [10]. Furthermore, one third of post-shunt deaths occur in the first 24 post-operative hours [3].

Factors such as patient weight and shunt size have been extensively investigated as smaller patient weight has been reported to be a risk factor for poor outcomes [3,4,6,12]. Smaller shunt size, a modifiable risk factor, has also been shown to impart greater risk of shunt failure and need for intervention [1,2,11]. By matching patients for weight and shunt size with controls, this study allows assessment of risk factors independent of these previously identified risk factors. Although previous studies have reported associations between heterotaxy syndrome and other congenital abnormalities with need for shunt intervention [2], this study was insufficiently powered to confirm these as risk factors for acute shunt complication.

The mechanisms of shunt dysfunction are varied and may include technical factors leading to mechanical distortion of the shunt or the pulmonary arteries, competitive flow states secondary to a patent ductus arteriosus or alternative source of pulmonary blood flow, and thrombosis. The presence of an alternate source of pulmonary blood flow, and whether or not to ligate the PDA at the time of surgery, remain topics of debate. Although an additional source of pulmonary blood flow may lead to competitive flow through the shunt and increased risk of shunt thrombosis [6], it can also provide flow in the event of acute shunt obstruction and prevent acute hypoxemia. Zahorec and colleagues determined that ligation of the PDA at the time of shunt placement was associated with increased need for re-intervention and mortality [7]. More recently, a multi-centre study including 1273 shunt procedures found no effect of PDA closure on morbidity or mortality [3], which is consistent with the findings of this study.

The first 30 days after systemic to pulmonary artery shunt placement are considered to be high risk for thrombotic complications [3], necessitating consideration of systemic thromboprophylaxis [8]. The most common anticoagulant used in the immediate post-operative period is UFH, although optimal dosage and timing of initiation are unclear. This study examined subjects' time to therapeutic anti-factor Xa levels and did not demonstrate any statistically significant relationship between acute shunt complication and time to therapeutic anticoagulation, intra-operative heparin doses nor *in-vivo* antithrombin levels.

Systemic steal due to over circulation resulting in decreased oxygen delivery with the risk of inadequate coronary, cerebral, gut and renal perfusion is another complication post systemic to pulmonary artery shunt; this was not a variable we chose to systemically evaluate due to sample size. We had one patient with hypotension and evidence of coronary ischemia that progressed to cardiac arrest and cannulation to venoarterial extracorporeal life support prior to his presentation with shunt thrombosis.

The most significant limitation of this study is the relatively small number of post-operative shunt complications that occurred during the study period (15 patients over 6 years) which limits the power of the study to detect significant differences. We did not apply Bonferroni correction, and as a result, we needed to minimize and prioritize the number of variables tested. RV-PA shunts were excluded from the cohort as these shunts are typically placed in the context of a Norwood procedure at our institution, are with rare exception 5mm in size, and do not have the challenge of competitive pulmonary blood flow.

Systemic to pulmonary artery shunts are critical in the palliation of children with limited pulmonary blood flow. This study demonstrates that despite therapeutic anticoagulation, smaller pulmonary artery size, a non modifiable risk factor, is associated with increased risk of post-operative shunt complication in the first 30 days regardless of patient weight and shunt size. Although there is great variability in management of these patients, and limited evidence on ways to mitigate the risks, our study contributes new prognostic information which may be considered when placing systemic to pulmonary artery shunts. Further studies with sufficient power are required to identify other associations of modifiable risk factors. Further investigation into the noted difference in the age at shunt between the two cohorts is warranted.

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Tables

Table 1: Overview of Shunt Complications.

Patient	Weight (kg)	Cardiac diagnosis	Shunt type	Shunt size (mm)	Mechanism of shunt failure	Intervention	Comment	Survival to hospital discharge
1	3	DORV/ TGA/ PA/ VSD/ RPA stenosis	Central shunt to MPA	3.5	Mechanical distortion of RPA	Shunt replacement and RPA plasty		Yes
4	9.6	RAI/ AVSD/ TGA/ TAPVR/ PS	Central shunt to LPA	4	Thrombosis	Shunt replacement	Multiple shunt complications; heterozygous for Factor V Leiden	No
5	3.8	TOF/ anomalous LAD from RCA	Right MBTS	4	Thrombosis	Shunt replacement with 4mm central shunt	Multiple shunt complications	Yes
6	3.5	PA/ IVS	Right MBTS	3.5	Thrombosis	UFH increase and fluid resuscitation		Yes
7	3.2	DILV/ PA	Right MBTS	3.5	Thrombosis	Shunt revision	Multiple shunt complications	Yes
8	2.7	TA/ VSD	Right MBTS	3.5	Thrombosis	Thrombus removal and shunt revision		Yes
9	3.4	DILV/ PA	Central shunt to LPA	3.5	Thrombosis	Cannulated for VA ECMO and then thrombectomy		Yes
10	3.1	TOF/ coronary artery anomaly	Right MBTS	3.5	Thrombosis	Shunt replacement		Yes
11	2.7	DILV/ PA	Right MBTS	3.5	Thrombosis	Thrombus removal and shunt revision		Yes
12	3.5	PA/ IVS	Central shunt to MPA	3.5	Thrombosis	Thrombus removal and shunt revision		Yes
13	3.4	PA/ IVS	Right MBTS	3.5	Thrombosis	VA ECLS and then shunt replacement		Yes
14	2.8	HLHS s/p Norwood-Sano	Right MBTS	3.5	Thrombosis	Percutaneous thrombectomy and RPA balloon dilatation		Yes
15	3.7	RAI/ DORV/ TGA/ AVSD/ PS	Central shunt to MPA	3.5	Thrombosis	Percutaneous thrombectomy and shunt stenting		No
16	3.4	PA/ IVS	Right MBTS	3.5	Thrombosis	Shunt revision		Yes
17	3.2	PA/ IVS	Right MBTS	3.5	Thrombosis	Shunt replacement with 4.0 RMBTS	Multiple shunt complications	Yes

Abbreviations: AT: Antithrombin; AVSD: Atrioventricular Septal Defect; DILV: Double Inlet Left Ventricle; DORV: Double Outlet Right Ventricle; HLHS: Hypoplastic Left Heart Syndrome; IVS: Intact Ventricular Septum; LAD: Left Anterior Descending; LPA: Left Pulmonary Artery; MBTS: Modified Blalock Taussig Shunt; MPA: Main Pulmonary Artery; PA: Pulmonary Atresia; PS: Pulmonary Stenosis; RAI: Right Atrial Isomerism; RCA: Right Coronary Artery; RPA: Right Pulmonary Artery; TA: Tricuspid Atresia; TGA: Transposition of Great Arteries; TAPVR: Total Anomalous Pulmonary Venous Return; TOF: Tetralogy of Fallot; UFH: Unfractionated Heparin; VSD: Ventricular Septal Defect

Table 2: Overview of Shunt Complications.

Variable	Shunt complication group (N=15)	Control group (N=15)	P value
Cohort Comparison			
Median weight at surgery (kg)	3.4 (3.0-3.5)	3.3 (3.0-3.7)	p=0.499
Median age at surgery (days)	15.0 (10.0-45.0)	8.0 (3.0-15.0)	p=0.037
Median shunt size (mm)	3.5 (3.5-3.5)	3.5 (3.5-3.5)	
Shunt type Right MBTS Central shunt to MPA Central shunt to RPA Central shunt to LPA	 10 (66.7%) 3 (20.0%) 0 (0%) 2 (13%)	 10 (66.7%) 3 (20.0%) 2 (13.3%) 0 (0%)	p=0.361

Surgical approach: Sternotomy Thoracotomy	 10 (66.7%) 5 (33.3%)	 11 (73.3%) 4 (26.7%)	p>0.999
Use of CPB	3	3	
Pre-determined Variables			
Total UFH bolus in OR (units/kg)[a]	100.0 (24-588)	57.7 (20-600)	p=0.389
Median diameter of target pulmonary artery (mm)	3.7 (3.3-4.4)	4.5 (4.0-5.1)	p=0.014
PDA ligated	6 (40%)	4 (26%)	p=0.439
First post-op antithrombin level	0.36 (0.32-0.47)	0.35 (0.32-0.50)	p=0.799
Alternative source of PBF post-operatively	12 (80%)	13 (86.7%)	p=1.00
Time to therapeutic anti-factor Xa (hours)	20.5 (13.0-50.3)	48.3 (24.2-96.4)	p=0.152
Post-operative bleeding	7 (46.7%)	4 (26.7%)	p=0.256
Non-cardiac congenital anomaly[b]	3 (20%)	3 (20%)	
Post-operative bacteremia[c]	0 (0%)	1 (6.7%)	p=1.00
Post-operative sternal wound infection[d]	3 (20%)	1 (6.7%)	p=0.598

Numerical data are expressed as median (1st quartile - 3rd quartile) except where otherwise indicated and categorical data are expressed as count (percentage).
CPB: Cardiopulmonary Bypass; LPA: Left Pulmonary Artery; MBTS: Modified Blalock Taussig Shunt; MPA: Main Pulmonary Artery; OR: Operating Room; PDA: Patent Ductus Arteriosus; RPA: Right Pulmonary Artery; UFH: Unfractionated Heparin

[a]Total UFH bolus in OR is presented as median (range)
[b]Non cardiac congenital anomalies in complication group were heterozygous for Factor V Leiden(n=1); X chromosome deletion and imperforate anus (n=1); absent right thumb, fused vertebral rib anomalies and missing ribs (n=1). Non cardiac congenital anomalies in the control group were chromosome 8 deletion (n=1); hypospadias (n=1); left upper limb and vertebral anomalies (n=1)
[c]Post-operative bacteremia and post-operative sternal wound infection together represent post-operative infection and are presented separately here.

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