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Single Ventricle Heterotaxy Syndrome patients with Systemic to Pulmonary artery shunts are at risk for early shunt failure after Ladd procedure

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Abstract

Background—Cardiac-specific risks and complications after Ladd procedure in patients with heterotaxy syndrome (HS) and intestinal rotational anomalies (IRA) are unknown. We sought to: **1)** describe rates of hospital mortality and early systemic to pulmonary (S-P) artery shunt failure after Ladd procedure in HS patients and **2)** explore risk factors associated with early shunt failure in HS patients with single ventricle (SV).

Methods—This retrospective study included all Ladd procedures performed from January 1999 to December 2012 on HS patients at a single center. Risk factors investigated for early S-P artery shunt failure included birth weight, gestational age, gender, age at and timing of Ladd procedure relative to cardiac surgery and shunt type.

Results—Ladd procedure was performed on 54 infants with HS and congenital heart disease. Hospital mortality for the entire cohort was 5.6% (3/54). Early shunt failure occurred in 19% (4/21) of HS infants with SV. Mean preoperative blood urea nitrogen (BUN) was higher in HS infants with early shunt failure (20 versus 12.5 mg/dL, $p=0.054$).

Conclusions—Single Ventricle, HS patients with S-P artery shunts are at risk for early shunt failure after Ladd procedure. A higher mean preoperative BUN is noted in HS subjects with early shunt failure. Careful risk-benefit analysis is indicated before recommending routine elective Ladd procedures in HS patients.

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Introduction

Failure of embryonic lateralization and left-right asymmetry results in an abnormal arrangement of thoracic and abdominal viscera, referred to as heterotaxy syndrome (HS) [1]. Forty to 90% of patients with HS have intestinal rotational anomalies (IRA) [2,3]. Patients with IRA are at risk for proximal small bowel obstruction, midgut volvulus and bowel necrosis [2–5].

Ladd procedure is widely accepted as the treatment for symptomatic IRA [6]. It includes detorsion of the bowel when volvulus is present, division of congenital fibrous bands, broadening the mesentery of the small bowel to potentially reduce future risk of bowel torsion and placement of small and large bowel in a non-rotated state.

Prophylactic Ladd procedure has been advocated by some centers for HS patients with IRA in an attempt to decrease the potential risk of midgut volvulus [7,8]. Early studies on HS patients with IRA reported low mortality and morbidity risk after elective Ladd procedures [8,9]. Therefore, many centers, including ours, perform an elective Ladd procedure on HS patients with IRA even if they are asymptomatic [7,11]. A more recent study reports a higher complication rate after the Ladd procedure and cautions against this practice [11]. This study, however, predominantly focused on gastrointestinal complications, particularly small bowel obstruction [11].

Unlike non-HS patients with IRA, HS patients frequently have complex congenital heart disease [1]. A palliative cardiac surgery often precedes the Ladd procedure. HS patients, particularly those with systemic to pulmonary (S-P) artery shunts and single ventricle (SV) physiology have a tenuous circulation, which may be perturbed by additional non-cardiac surgeries.

This single center retrospective study was therefore conducted with the following objectives:

1. Describe rates of hospital mortality and early S-P artery shunt failure after Ladd procedure in HS patients with SV.
2. Explore risk factors associated with early shunt failure.

Material and Methods

Study Design, Site, and Subjects

This retrospective study was conducted at Columbia University Medical Center, a tertiary care academic center in New York City, on HS infants with congenital heart disease who underwent Ladd procedure between January 1, 1999 and December 31, 2012. Study subjects were primarily admitted to our neonatal intensive care unit.

It is our center's practice to screen all HS patients for IRA and to perform an elective Ladd procedure on those who screen positive, usually during the same hospitalization or rarely after discharge and when clinically stable. Patients who develop signs of intestinal obstruction or volvulus undergo an emergent Ladd procedure.

Subjects with HS who underwent Ladd procedure were identified by cross-referencing administrative databases from the Divisions of Neonatology and Pediatric Surgery. Included subjects were those who were diagnosed with HS and congenital heart disease, positively screened for anomaly of rotation by an upper gastrointestinal (UGI) contrast study, and who underwent Ladd procedure by pediatric surgeons at our institution. Excluded subjects were HS infants without congenital heart disease and those who did not receive Ladd procedure at our institution. Also excluded were subjects in whom IRA was associated with other gastrointestinal anomalies e.g. omphalocele. The institutional review board for Columbia University Medical Center approved this study with a waiver of informed consent.

Definitions

For the purpose of this study, congenital heart disease was defined as an anatomic abnormality of the heart present from birth. Isolated vascular abnormalities that did not require surgical intervention e.g. interrupted inferior vena cava were not considered congenital heart disease. Lesions with single ventricle anatomy and following a univentricular pathway were defined as SV.

IRA was identified by an UGI contrast study. A single pediatric radiologist (BL) reviewed all UGI studies to confirm the presence of IRA. S-P artery shunt failure was defined as an urgent need for a trans-catheter or surgical revision of S-P artery shunt due to severe hypoxemia.

Operative Management

At our institution, S-P artery shunts are placed either by lateral thoracotomy or median sternotomy, based on anatomy and surgeon preference. Ladd procedure is performed usually by open laparotomy and standard techniques are utilized. General pediatric anesthesiologists, and rarely cardiac anesthesiologists, provide anesthetic management during Ladd procedures.

Perioperative Management

At our center, S-P artery shunt patients receive intravenous maintenance fluids (of 100 ml/Kg) with dextrose and standard electrolytes in the perioperative period. Intraoperative fluid management includes continuation of maintenance fluids and/or addition of normal saline or Ringer's lactate as determined necessary by the Anesthesia team.

Our current practice is to initiate oral ASA on postoperative day 1 after shunt placement at a dose of 20mg/day. Earlier in the study period, ASA at the same dose was given only after full enteral feeds were established. Subcutaneous Enoxaparin is provided only if enteral feedings are contraindicated e.g. necrotizing enterocolitis or if anticoagulation therapy is indicated for a concomitant morbidity e.g. venous or arterial thrombosis. Anticoagulation strategy is often but not uniformly modified following non-cardiac operations based on surgeon preference: ASA is replaced with subcutaneous Enoxaparin on the day of the surgical procedure and continued until enteral feeds are reinitiated when ASA is reintroduced.

Outcomes

The primary endpoint was hospital mortality and/or S-P artery shunt failure requiring an urgent surgical or trans-catheter intervention within 72 hours of the Ladd procedure.

Study Procedures

Hospital medical records, operative, radiology, echocardiogram reports were reviewed for patient demographics, hospital mortality, description of cardiac lesion and surgery, laboratory values, medication use, and post-surgical complications following the Ladd procedure.

Statistical Analysis

Descriptive statistics were performed to explore the distribution of variables of interest, such as birth weight, gestational age, age at Ladd procedure, time from first cardiac surgery to Ladd procedure, gender, race, preoperative diuretic and anticoagulant use, perioperative blood urea nitrogen (BUN) and serum creatinine, S-P artery shunt size and type, and whether Ladd procedure was performed emergently or electively.

Tabular analysis was performed to evaluate the relationship between variables of interest and those infants with and without the outcome of early shunt failure postoperatively. Wilcoxon Rank-Sum tests were used for continuous variables and Fisher's exact tests were used for categorical variables, as appropriate. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Results

Eighty- six infants were admitted with a diagnosis of HS to our institution during the study period (Figure 1). Excluded infants (n=32) were those in whom a congenital heart disease was not identified (n=5), an UGI was not done (n= 10), an IRA was ruled out (n= 8) or those in whom Ladd procedure was not performed at our institution (n=9). Fifty-four infants with HS and congenital heart disease underwent Ladd procedure for IRA at our center from 1/1/1999 to 12/31/2012 and were included in the final analysis.

Sixty-one percent (33/54) of subjects in this series were males. The median age at Ladd procedure was 21 days (IQR15-57). Cardiac lesion and surgery characteristics of the entire cohort are shown in Table 1. The most common cardiac defect was a right-sided obstructive lesion (35%), followed by partial or total anomalous pulmonary venous return (28%). Forty-five (83%) infants in this cohort had a cardiac surgical intervention prior to the Ladd procedure. Twenty-six infants (48%) had S-P artery shunt placement of which 21 infants followed a SV palliation pathway.

Three of 54 (5.5%) patients had an emergent Ladd procedure performed for symptoms concerning for volvulus. One infant of the 3 had confirmed volvulus and underwent partial bowel resection. Two subjects manifested symptoms within the first week of life, including the patient with volvulus; the third patient was nearly 4 years old when symptoms appeared. The remaining 51 infants underwent Ladd procedure electively.

Three infants (5.6%) in this cohort died during initial hospitalization (Table 2). Two infants died of necrotizing enterocolitis, fulminant sepsis and multiorgan failure. One other infant sustained cardiopulmonary arrest after acute, profound hypoxemia during transport to the intensive care unit after an elective Ladd procedure. Death in this patient was presumed to be secondary to S-P artery occlusion, although an autopsy was never performed to confirm. Three additional HS infants with SV underwent surgical revision of S-P artery shunts for shunt occlusion. Thus, early S-P artery shunt failure occurred after a Ladd procedure in 4 of 21 HS infants (19%) with SV physiology. In all 4 subjects, Ladd procedure was performed electively.

Subgroup analysis of the 21 subjects with SV and S-P artery shunt is shown in Table 3. In this sample, infants who had early shunt failure had a higher preoperative BUN (20 versus 12.5 mg/dL) $p = 0.054$, OR = 1.2, CI₉₅ (0.99, 1.48). Neither postoperative BUN nor pre nor postoperative creatinine was significantly different between those with and without the outcome.

Four of 54 infants (7%) in our series developed small bowel obstruction requiring surgery at a median of 126 days after the Ladd procedure (range-30–503 days).

Comment

To our knowledge, this is the largest study to date, to investigate the risk of early S-P artery shunt failure after Ladd procedure in children with HS.

We evaluated the outcomes of hospital mortality and early S-P artery failure after the Ladd procedure in HS patients. Mortality rate after an elective Ladd procedure in HS patients is variable (0–22%), with higher rates noted in HS patients with functional single ventricles [7–12]. The 5.6% mortality rate in our series is within the range reported previously, however our study includes both elective and emergent Ladd procedures.

Our study's primary finding is a 19% early S-P artery shunt failure rate after Ladd procedure in HS patients with SV. Only one study has previously described S-P artery shunt failure associated with Ladd procedure in HS patients, but this study included only 2 single ventricle patients, both of whom had S-P artery shunt thrombosis [12]. Our institution's S-P artery shunt occlusion rate of 8% in all patients with S-P artery shunts makes our findings all the more relevant.

An S-P artery shunt is placed in infants whose cardiac anatomy, age or weight may not permit a one-stage complete repair [13]. Pulmonary blood flow is dependent upon shunt patency and hence occlusion of an S-P artery shunt can cause life-threatening hypoxemia. S-P artery shunt occlusion is not uncommon; an in-hospital occlusion rate of 6.5–13.5% has previously been reported [14,15]. Various factors increase risk for shunt occlusion: lower weight, younger age, smaller shunt size and surgical approach via thoracotomy [14,15].

Lowering the pressure gradient or increasing resistance across an S-P artery shunt may potentially decrease flow across the shunt and promote thrombus formation. In our study, as preoperative BUN was higher in the subjects with early shunt failure, we speculate that

shunt flow may have been decreased due to sub-optimal hydration status. Perioperative fluid balance was not available on all subjects and postoperative serum BUN and creatinine were measured after shunt revision in the subjects with shunt failure. Hence, it is not possible to determine conclusively, based on the available data whether suboptimal perioperative hydration status contributed to shunt failure.

Neonates exposed to cardiopulmonary bypass and especially those with SV physiology are at elevated risk for postoperative thrombotic events [16–18]. Immature hemostatic mechanisms, developmental deficiencies and postoperative depletion of circulating pro and anticoagulant protein levels result in a diminished capacity to suppress thrombin generation after cardiac surgery [16–19]. Hence a hypercoagulable state exists after cardiac surgery that may exhibit resistance to anticoagulation [20,21]. We speculate that additional inciting events such as surgical trauma may exacerbate a baseline prothrombotic state and increase risk for S-P artery shunt thrombosis in the perioperative period. Coagulation profile and hypercoagulability markers were not measured in our series and hence we were unable to confirm the role of hypercoagulability in patients who experienced early shunt failure.

There is broad agreement that HS patients with symptomatic IRA require Ladd procedure [7–11]. However, there is no consensus for the management of asymptomatic IRA in HS patients. As a result, considerable controversy exists and widespread practice variation is noted [10]. Some centers screen all HS patients for IRA and perform an elective Ladd procedure on those who test positive [7–10]. Others adopt a conservative approach and defer from screening for IRA unless the patient with HS develops symptoms [22]. This divergence of practice results from unclear benefits of elective Ladd procedures in asymptomatic HS patients. A wide spectrum of IRA anomalies exist not all of which pose equivalent risk of volvulus [23,24]. Hence, the benefit of an elective Ladd procedure in an asymptomatic patient with an IRA variant which has low-risk potential for volvulus is likely minimal. However, the risks and complications of electively or emergently performed Ladd procedure are clear and have been previously reported [25]. The most common complication after Ladd procedure includes a significant risk of recurrent small bowel obstruction requiring surgical intervention in 5–14% of children [8,25–27]. Furthermore, the risk of recurrent mid-gut volvulus, although rare, is not abolished after the Ladd procedure [27,28].

Our experience underscores the importance of assessing the risk-benefit of an elective Ladd procedure in asymptomatic HS patients particularly in those with S-P artery shunts and SV. Our results indicate that an individualized approach in these patients is warranted. Our current practice is to perform a screening UGI on all patients with HS when stable. Patients who screen positive for IRA and who do not have an S-P artery shunt undergo an elective Ladd procedure when they are stable from a cardiovascular standpoint and usually during the same hospitalization. Patients who have an S-P artery shunt undergo an elective Ladd procedure 3–4 months after S-P artery shunt take-down and/or Glenn procedure. The Glenn procedure, performed at 4–6 months of age increases oxygen saturation, decreases ventricular volume load and permits a more stable circulation.

The risk of volvulus is greatest in neonates and declines with age but is not eliminated [28–30]. Hence, our center follows a conservative approach and offers elective Ladd procedure

to HS infants despite a diminishing risk of volvulus in later infancy and childhood. While our institution favors an elective Ladd procedure in all IRA variants, further risk stratification and asymptomatic patients with low risk IRA variants may probably be managed with close surveillance and without the need for an elective Ladd procedure.

There are several limitations to this study including its retrospective design with its inherent disadvantages. Our study may not have been powered to detect variables of interest that could potentially influence the primary endpoints. The extended study period may not reflect recent improvements in the performance of non-cardiac procedures in HS patients including anesthetic delivery, fluid management in the perioperative period and a better appreciation of circulatory balance and anticoagulation in S-P artery shunt patients. Anticoagulant use and whether it was held prior to the Ladd procedure was not available on all patients and hence we were not able to identify if perioperative anticoagulant use was protective. This study was limited to Ladd procedure in HS patients and does not answer if similar risks apply when HS patients undergo other non-cardiac surgeries e.g., gastrostomy tube placement. This study does not answer whether there is heightened risk of shunt failure in HS patients compared to non-HS patients. This study does not answer whether it is safe to defer Ladd procedure until after S-P artery shunt take-down and Glenn procedure.

Conclusion

Single Ventricle, HS patients with S-P artery shunts are at risk for early shunt failure after Ladd procedure. Careful risk-benefit analysis is indicated before recommending routine elective Ladd procedures in HS patients.

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Figure 1.
Flow diagram of HS patient population during the study period.

Table 1

Cardiac lesion and surgery prior to Ladd procedure

Primary Cardiac Defect Class- N= 54	Specific Cardiac Lesion	Most recent cardiac surgical intervention prior to Ladd procedure- N=45
AVC ^a and Septal Defects-8	Common AVC-4 ASD ^b -1 VSD ^c and ASD-3	Pulmonary artery banding-1 No cardiac surgery prior to Ladd procedure-3 ASD closure-1 Pulmonary artery banding-1 No cardiac surgery prior to Ladd procedure-2
Right Ventricular Outflow Tract Obstruction-19	Pulmonary valve stenosis-7 Pulmonary atresia-12	S-P ^d artery shunt-6 No cardiac surgery prior to Ladd procedure-1 S-P artery shunt-10 Glenn-1 Fontan-1
Left Ventricular Outflow Tract Obstruction -11	Hypoplastic aortic arch-2 Common AVC/Coarctation of Aorta-2 Subaortic Stenosis-1 Hypoplastic left heart syndrome-4 DORV ^f , TGA ^g , hypoplastic aortic arch-1 Coarctation of Aorta and pulmonary valve stenosis-1	Aortic arch reconstruction-2 Coarctation repair/pulmonary artery banding-2 Ross-Konno-1 Norwood-Sano-2 Norwood- BT ^e Shunt-2 Arterial Switch Procedure, aortic arch reconstruction, VSD closure-1 No cardiac surgery prior to Ladd procedure-1
Anomalous pulmonary venous drainage-3	TAPVR ^h -2 PAPVR ⁱ -1	TAPVR repair-2 PAPVR repair-1
Anomalous pulmonary venous drainage with right ventricular outflow tract obstruction-12	TAPVR+PS ^j -5 TAPVR+PA ^k -7	TAPVR repair+ S-P artery shunt-1 S-P artery shunt-1 TAPVR repair-1 Glenn-1 No cardiac surgery prior to Ladd procedure-1 TAPVR repair+ S-P artery shunt-6 Glenn-1
Other-1	L-TGA ^l , Ebstein anomaly-1	No cardiac surgery prior to Ladd procedure-1

Abbreviations used in Table 1: a: AVC- atrioventricular canal, b: ASD- atrial septal defect, c: VSD-ventricular septal defect, d: S-P -Systemic to pulmonary, e: BT- Blalock Taussig, f: DORV- Double outlet right ventricle, g: TGA- Transposition of the great arteries, h: TAPVR- Total anomalous pulmonary venous return, i: PAPVR-Partial anomalous pulmonary venous return, j: PS- Pulmonary stenosis, k: PA-Pulmonary atresia, l: L-TGA- levo- Transposition of the great arteries.

Table 2
Case summaries of Heterotaxy syndrome patients with primary outcome of hospital mortality and/or early shunt failure

Patient No.	Cardiac Lesion	Cardiac Surgery	IRA ^a and Ladd Procedure Summary	Complication	Hospital mortality
1	RAI ^b , CAVC ^c , DORV ^d , TGA ^e , PS ^f	3.5 mm right modified B-T ^g shunt on DOL ^h 4.	Elective Ladd procedure 12 days after cardiac surgery.	Cardiopulmonary arrest 72 hours after Ladd procedure. BT shunt occlusion was diagnosed on Echocardiography and ductus arteriosus was reopened with PGE-1. A 3.5 mm central shunt was placed 9 days later. Thrombus was not noted in the original shunt.	No
2	RAI, CAVC, DORV, TGA, PA ⁱ , TAPVR ^j	TAPVR repair, 3.5 mm central shunt on DOL 2.	Elective Ladd procedure 10 days after cardiac surgery.	Cardiopulmonary arrest on transport from operating room after Ladd procedure.	Yes
3	LAI ^k , CAVC, small left ventricle, juxtaductal coarctation, PS	Listed for cardiac transplantation.	Ladd procedure at 5 days of age for bilious aspirates. No volvulus was identified.	Necrotizing enterocolitis and multi-organ failure secondary to Citrobacter koseri sepsis 14 days after Ladd procedure.	Yes
4	RAI, CAVC, DORV, TGA, PS, TAPVR	TAPVR repair, 3.5 mm central shunt on DOL 1.	Elective Ladd procedure 27 days after cardiac surgery.	Shunt occlusion diagnosed on arrival to ICU ^l . Emergent 3.5 mm central shunt revision performed. Thrombus was identified in the original shunt.	No
5	RAI, CAVC, DORV, TGA, PA	4 mm right modified B-T shunt on DOL 15.	Elective Ladd procedure 14 days after cardiac surgery.	Shunt occlusion diagnosed on arrival to ICU. Emergent 3.5 mm right modified B-T shunt revision performed. Thrombus was identified in the original shunt.	No
6	RAI, CAVC, DORV, TGA, PS	3.5 mm right modified B-T shunt placement on DOL 16.	Elective laparoscopic Ladd procedure 7 days prior to cardiac surgery.	Fulminant necrotizing enterocolitis and multisystem organ failure on DOL 19.	Yes

Abbreviations used in Table: a: IRA- intestinal rotational anomaly, b: RAI- right atrial isomerism, c: CAVC- common atrioventricular canal, d: DORV- double outlet right ventricle, e: TGA- transposition of the great arteries, f: PS- pulmonary stenosis, g: B-T- Blalock-Taussig, h: DOL- day of life, i: PA-pulmonary atresia, j: TAPVR- total anomalous pulmonary venous return, k: LAI- left atrial isomerism, l: ICU- intensive care unit.

Table 3Risk factors for early S-P^a artery shunt failure in HS^b infants with Single Ventricle

Variable	Outcome		OR	p
	Yes N=4	No N=17		
Male gender N (%)	2(50)	15(71)	NA	0.57
African American Race N (%)	0 (0)	3(18)	NA	0.7
Birth weight, grams, mean ($\pm$ sd)	2757($\pm$ 265)	3250($\pm$ 420)	NA	0.08
Gestational age, weeks, mean ($\pm$ sd)	39($\pm$ 1)	38.5($\pm$ 1.5)	NA	0.06
Age at Ladd procedure, days, median (IQR) ^c	21.5(14–28)	18(15–31)	NA	0.86
Time between cardiac surgery and Ladd procedure, days, median (IQR)	13(11–20.5)	12(8–19)	NA	0.62
Preoperative Serum BUN, mg/dL, mean ($\pm$ sd)	20 ($\pm$ 7.3)	12.5($\pm$ 5.7)	1.2, CI ₉₅ (0.99, 1.48)	0.054
Preoperative serum Cr ^e mg/dL, mean ($\pm$ sd)	0.55 ($\pm$ 0.25)	0.46($\pm$ 0.16)	NA	0.4
Postoperative serum BUN, mg/dL, mean ($\pm$ sd)	17.7 ($\pm$ 4.7)	13($\pm$ 4.5)	NA	0.088
Postoperative serum Cr, mg/dl, mean, ($\pm$ sd)	0.5 ($\pm$ 0.17)	0.38($\pm$ 0.13)	NA	0.19
Preoperative oxygen saturation %, median (IQR)	73(62–80.5)	83(77–85)	NA	0.07
Shunt size, 3.5mm vs. 4mm N (%)	3(75)	6(35)	NA	0.42
Central Shunt vs. BT ^f shunt N (%)	2(50)	7(41)	NA	1
Preoperative diuretic exposure N (%)	4(100)	15(88)	NA	1
Anticoagulation held 24h prior to surgery	2(50)	11(65)	NA	0.65

Abbreviations used in Table 3: a: S-P- systemic-to-pulmonary, b: HS- heterotaxy, c: IQR-interquartile range, d: BUN- blood urea nitrogen, e: Cr: Creatinine, f: B-T- Blalock-Taussig.