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Catheterization-Based Intervention in Low Birth Weight Infants Less than 2.5 kg with Acute and Long-Term Outcome

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Background: The number of low birth weight infants with congenital heart disease is increasing and catheterizations may have an increased risk for mortality and morbidity. Objectives: We investigate the outcome and complications of cardiac catheterizations in infants weighing < 2.5 kg. Methods: Retrospective review of catheterization records from 1995 to 2010 in infants weighing < 2.5 kg. The demographics, procedure, outcome, and follow-up data were collected. Results: Of 101 catheterizations performed in 88 patients, 45 (45%) catheterizations were interventional. Balloon atrial septostomy ($n = 23$), pulmonary valvuloplasty (14), aortic valvuloplasty (4), stent placement (3), balloon angioplasty (2), and temporary pacemaker insertion (1) were successfully performed. Balloon atrial septostomy was performed with pulmonary or aortic valvuloplasty in two catheterizations. Infants < 2.5 kg had higher significant adverse event rate that those 2.5−3.5 kg (13% versus 6.6%, $P < 0.05$). No procedural death was noted. Significant adverse events ($n = 13$) included cardiopulmonary resuscitation three, vascular six, arrhythmia three, and apnea requiring intubation one. On median follow-up of 3 years (0.03 to 14), $n = 69$, mortality rate was 36%. In six patients with valvar pulmonary stenosis with median follow-up of 6 years (0.75–13), four (67%) did not require re-intervention. Of two patients with aortic stenosis, one did not require repeat intervention for 6 years (last follow-up). Conclusion: Interventional catheterization is feasible with low procedural morbidity and mortality in high risk infants < 2.5 kg. Catheterization primarily serves as a palliative procedure to stabilize infants for definitive treatment. Balloon valvuloplasty may be effective for isolated valvar pulmonary stenosis in infants < 2.5 kg. © 2013 Wiley Periodicals, Inc.

Key words: cardiac catheterization; <2.5 kg; intervention; complications

INTRODUCTION

Infants with congenital heart disease (CHD) have a higher incidence of low birth weight (LBW) [1]. In the current era of improved neonatal care, mortality of LBW infants continues to decline [2]. However, mortality for premature and LBW infants undergoing surgery for CHD remain high [3,4]. Therefore, catheter-based interventions as a palliative and therapeutic option have been increasingly utilized to improve the outcome of these high risk infants. Furthermore, technical feasibility, outcome and complications of cardiac catheterization continue to be a concern because of small infant size and weight. Few large studies reporting their catheterization experience have shown increased risk of mortality and vascular compromise in LBW infants [5–7]. However, the long term outcome of high risk LBW infants with complex CHD undergoing catheterization has not been adequately

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evaluated. We report the acute- and long-term outcome, and significant adverse events (SAE) of cardiac catheterizations in infants weighing < 2.5 kg from a single center.

MATERIALS AND METHODS

Retrospective review of patients weighing < 2.5 kg who underwent cardiac catheterization from 1995 to 2010 was performed with the approval from Institutional Review Board. The catheterization reports, medical records, procedural, and follow-up data were reviewed in all patients. The study group was divided by procedure types as diagnostic or interventional for analysis. The angioplasty of pulmonary and aortic valve was performed using standard techniques similar to that in larger infants. The balloon size for balloon pulmonary valvuloplasty (BPV) and balloon aortic valvuloplasty (BAV) was chosen with ratio of balloon diameter to the annulus being 100–150% and 80–100%, respectively. The procedural success based on specific intervention were defined as; Balloon atrial septostomy (BAS)—decrease in gradient across the atrial septum, or improved oxygen saturation, or improved flow across the atrial septum by echocardiography. BPV–decreased right ventricle / systemic pressure ratio, or improved flow across the pulmonary valve with ability to successfully wean off prostaglandins. BAV—increased forward flow through the aortic valve, decrease in gradient of at least 40% and/or ability to wean prostaglandin infusion or inotropic support [8]. Stenotic vessel angioplasty/stent–improvement in stenotic segment greater than 50% of its original size or improved contrast/blood flow. Regarding anticoagulation during the catheterization, intravenous heparin (initial dose 75−100 units per kg) was routinely used for interventional left heart catheterization, and activated clotting time was monitored every 30 minutes to maintain activated clotting time longer than 250 seconds. However, heparin was not always used for diagnostic or interventional right heart catheterization. Head ultrasound was routinely obtained in the neonatal intensive care unit prior to the catheterization and heparin was avoided for elevated baseline activated clotting time. SAE was defined as death, cardiopulmonary resuscitation, and complications including hemodynamic instability, respiratory compromise, cardiac perforation, vascular injury, blood loss, arrhythmias, atrioventricular block, and others that caused significant morbidity, leading to medical and surgical interventions, and/or extended length of stay. As a reference, we collected the SAE data in infants weighing 2.5−3.5 kg undergoing cardiac catheterization during the same study period. Long-term follow-up data were divided into two groups: (1) intervention as a primary therapeutic option (BAV and BPV), and (2) diagnostic and or intervention as a palliative procedure. Statistical analysis was performed using SPSS software for PC (version 19.0) (SPSS, Chicago, IL). Continuous variables were reported as median and range, and nominal variables were reported as number (percentage). Independent student's *t* test and Chi-square test were used to compare parameters between groups.

RESULTS

Patients and Diagnoses

We identified 101 catheterizations in 88 patients weighing < 2.5 kg at the time of procedure. Of these, 56 were diagnostic and 45 catheterizations were interventional procedures. At the catheterization, the median (range) age, gestational age, and weight was 9 days (0−97), 34 weeks (28−39), and 2.2 kg (0.98−2.5), respectively (Supporting Information Table I). The most common diagnoses (Supporting Information figure) are transposition of great arteries, $n = 13$, followed by PS 11, hypoplastic left heart syndrome eight, double outlet right ventricle eight, pulmonary atresia with intact ventricular septum eight, pulmonary atresia with ventricular septum defect eight, tetralogy of Fallot seven, and interrupted aortic arch six. Forty five interventions were performed in 41 patients (Fig. 1). The most common interventions were BAS and/or atrial septal dilation, $n = 23$, BPV, $n = 14$, and BAV, $n = 4$. As compared to venous access obtained in 93% of catheterizations, arterial access was obtained in 25%.

Hemodynamics and Interventions

Patient demographics and comparison between the diagnostic and interventional groups (Supporting Information Table I). Technical characteristics, hemodynamics, and interventions are summarized in Tables I and II. The diagnostic procedures were performed to delineate pulmonary arterial anatomy, confluence, collaterals, and pulmonary venous drainage. The most common interventions were BAS, and angioplasty of aortic and pulmonary valves. All interventions were acutely successful. BPV was performed in 14 patients (Table I). The ratio of systolic right ventricle pressure to systolic systemic pressure was significantly decreased after BPV in most patients. However, hemodynamic assessment of right-sided pressures might be affected by the presence of widely open ductus arteriosus. Six patients underwent BPV for isolated valvar PS. Remaining eight patients had complex PS with associated other CHD and/or additional sub and supravalvar stenosis (Table I). BAV was performed successfully in four patients (Table I). Three patients underwent BAV for isolated valvar AS. Twenty-three BAS and/or atrial septal dilation were performed in 20 patients successfully and three patients required repeat

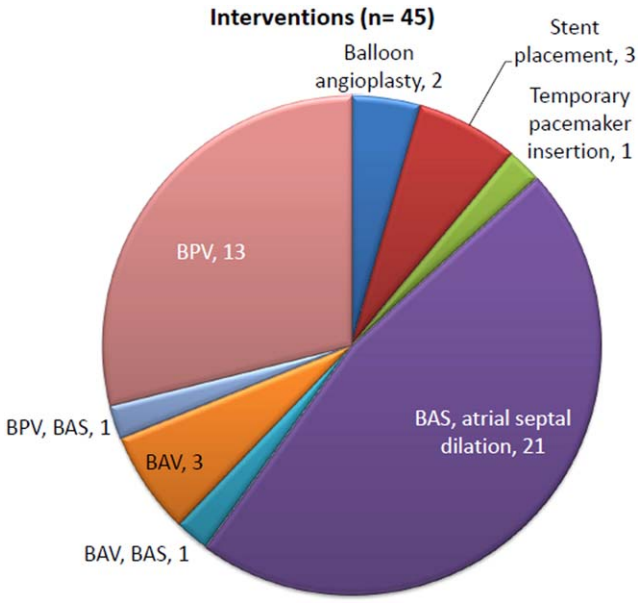


Fig. 1. Interventions. BPV, balloon pulmonary valvuloplasty; BAS, balloon atrial septostomy; BAV, balloon aortic valvuloplasty. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

septostomy prior to palliative or definitive surgery (Table II). The remaining interventions are listed in Table II.

Complications

Table III summarizes the SAE in infants weighing <2.5 kg. The overall SAE rate in infants weighing < 2.5 kg was higher than that in those weighing 2.5−3.5 kg (13% versus 6.6%, $P < 0.05$, Supporting Information Table II). The incidence of vascular complications was significantly higher in infants weighing < 2.5 kg than those weighing 2.5–3.5 kg (6% vs. 0.9%, $P < 0.05$). Among the infants < 2.5 kg, the SAE rates between diagnostic and interventional groups were comparable (11% vs. 16%, $P = 0.56$). There was no procedural death. Cardiopulmonary resuscitation was performed briefly in three patients among the interventional group and they continued to have successful procedure. One patient (Pt 7) with valvar PS had endotracheal tube displacement and bradycardia requiring chest compression and re-intubation followed by successful angioplasty. The second patient (Pt 13), following BPV had cardiac arrest requiring resuscitation with chest compression and one dose of epinephrine. The third patient (Pt 39), following stent placement in vertical vein for obstructed total anomalous pulmonary venous return experienced bradycardia because of inadvertent extubation requiring chest compression and re-intubation. Arrhythmia ($n = 3$) included supraventricular tachycardia treated with adenosine in two patients (Pt 31) and transient heart block requiring no intervention in one patient. Among vascular compromise ($n = 6$), three patients were treated with heparin for lost femoral arterial pulse (Pt 2). All of them recovered with good perfusion and recovery of distal pulses 48 hrs later. Two had vascular injury to inferior vena cava (IVC); one patient (Pt 5) underwent pulmonary angioplasty and repeat catheterization for BPV revealed intimal damage of hepatic portion of IVC. This did not require any intervention and was presumed to be related to previous catheterization. Second patient underwent diagnostic catheterization for severe PS, patent ductus arteriosus and multiple ventricular septal defects without complications. One week later repeat catheterization was performed for desaturations to attempt BPV. This revealed IVC occlusion below renal veins and BPV was performed with right internal jugular venous approach. IVC thrombus was presumed to be related to prior catheterization and extension of thrombus from right femoral vein or related to previous umbilical venous line placement. One patient (Pt 33) with hypoplastic left heart syndrome following Hybrid stage 1 procedure underwent BAS for atrial restriction using right femoral vein. Three weeks later, a stent was placed for re-coarctation using left femoral vein prograde allowing controlled stent delivery through a large sheath and to prevent arterial vessel injury. Repeat catheterization 3 weeks later for recurrent atrial restriction revealed bilateral femoral vein occlusion requiring stent placement in the atrial septum using Hybrid approach. On further review, among six patients with vascular compromise, heparin was administered in only one patient with IVC damage. Head ultrasound on all patients was normal and heparin was withheld in one because of prolonged baseline ACT. In the remaining four patients, heparin was not given based on the operating physician's preference.

Long-Term Outcomes

The long-term outcome is summarized in Fig. 2. Follow-up data were available in 69 patients (78%), with a median follow-up of 3 years (range: 2 weeks to 14 years). In the intervention group; with a median follow up of 7 years (range: 9 months–13 years), five of 46 patients (10%), four with isolated valvar PS and one with valvar aortic stenosis have been hemodynamicaly stable without need for re-intervention at last follow-up. The remaining patients had re-intervention/definitive or staged surgical palliation ($n = 30$) and total deaths ($n = 11$) (Tables I and II). In the diagnostic group; 32 of 45 patients were available for follow-up. Twenty-five patients underwent palliative or corrective surgery and 17 (53%) were doing well at last follow-

TABLE I. Balloon Valvuloplasty

Pt	Wt (kg)	Age (day)	Diagnoses	Re-intervention Age	Re-intervention Type	Last follow-up Age	Last follow-up ECHO findings (Grad PV mm Hg)
Balloon pulmonary valvulopalsty							
1	1.0	11	Isolated valvar PS		None	13y	Alive Mild PI, Grad 21
2	2.3	0	Isolated valvar PS		None	8y	Alive No PI, Grad 16
3	1.6	1	Isolated valvar PS		None	7y	Alive Trivial PI, no PS
4	1.6	35	Isolated valvar PS		None	9m	Alive Mild PI, Grad 22
5	1.6	1	Isolated valvar PS	78d 6m	BPV surgery	6y	Alive Free PI, no PS
6	1.6	3	Isolated valvar PS	45d	BPV	16m	Alive Trivial PI, Grad 20
7	2.2	69	Sub/Supravalvular PS	84d	Surgery	7m	Alive Free PI, no PS
8	2.5	15	Supravalvular PS / AS, Williams*	4m	Surgery	11y	Alive Mod PI, Grad 21
9	1.2	27	Valvar/subvalar PS	7m	BPV	7m	Alive Free PI, Grad 31
10	1.8	13	DORV,PS,Goldernhar's	Lost to follow-up			
11	2.5	11	VSD, PS	8m	Surgery	10m	Alive Free PI, Grad 19
12	2.4	13	VSD, ASD, ASD, PS	16d	Surgery	3y	Alive Free PI, no PS
13	2.1	66	VSD, PS, Trisomy 10, monosomy 5	99d	Surgery	170d	Death
14	1.9	32	TOF, PS, Trisomy 18		None	35d	Death

Pt	Wt (kg)	Age (day)	Diagnoses	Re-Intervention Age	Re-Intervention Type	Last follow-up Age	Last follow-up Comment
Balloon aortic valvulopalsty							
15	2.3	90	Isolated valvar AS		None	6y	Alive Trivial AI, no AS
16	2.5	2	Isolated valvar AS	68d	Surgery	8y	Alive
17	2.2	1	Isolated valvar AS	Lost follow-up			
18	2.5	97	HLHS, EFE	163d 182d	BAV OHT	6y	Alive

Pt 10 underwent concomitant balloon atrial septostomy at the same catheterization. Pt 18 underwent concomitant balloon atrial septostomy at the same catheterization.

up. There were eight deaths in this group of various causes. In addition, there were six deaths in patients awaiting initial treatment. In the entire cohort available for follow-up ($n = 69$), there were total of 25 deaths (36%); complex CHD comprising Tetralogy of Fallot or double outlet right ventricle associated with pulmonary atresia and hypoplastic pulmonary arteries were the majority 10 (40%), followed by single ventricle pathology six (24%) and CHD associated with chromosomal anomalies in six (24%) patients. Figure 2 summarizes various causes of death with sepsis, nectrotizing enterocolitis, hypoxemia, heart failure with multi-organ failure as leading cause for mortality.

DISCUSSION

Catheter interventions in LBW infants have been facilitated with rapid advances in cardiac catheterization techniques, miniaturization, and improvement in catheter design and equipment. Although surgical outcome of CHD continues to improve in LBW infants, there is still significant morbidity and mortality [3,4]. Catheter interventions can palliate those high risk infants to optimize weight gain, leading to successful surgery with less morbidity and mortality. Our cohort had near equal share of interventional (44%) and diagnostic catheterization (56%) procedures. There was no procedure related deaths. Intervention predominantly

TABLE II. Other Interventions

Pt	Weight (kg)	Age (day)	Diagnoses	Surgery	Last follow-up Age	Last follow-up Outcome
Balloon Atrial Septostomy and Atrial Septal Dilation						
10	1.8	13	DORV, PS	Lost to follow-up		
18	1.9	22	HLHS, EFE	OHT (182 do)	6y	Alive
	2.5	97				
19	1.4	4	Tricuspid atresia	PAB (38 do), Hemi-Fontan (10 mo), Fontan (2 yo)	3y	Alive
20	2.3	3	PA/IVS, RVDCA	mBTS (11 do), Hemi-Fontan (6 mo), Fontan (2yo)	8y	Alive
21	1.7	1	TGA	ASO (20 do)	5y	Alive
22	2	3	TGA	OHT (61 do)	11y	Alive
23	2.3	0	TGA	ASO (7 do)	3y	Alive
24	2.4	12	TGA	ASO (124 do)	7y	Alive
25	2.5	3	TGA	ASO (9 do)	7y	Alive
26	2.5	3	TGA	ASO (18 do)	11y	Alive
27	2.1	6	TGA	ASO (32 do)	11m	Alive
	2.1	8				
28	2	0	TGA	ASO (40 do)	11y	Alive
	2	31				
29	1.8	14	PA/IVS, RVDCA	NA	10y	Alive
30	1.6	5	TGA	None	14d	Death
31	1.9	8	TGA, IAA	ASO, arch repair (40 do)	86d	Death
32	2.3	3	PA/IVS, MAPCA	Unifocalization, systemic-pulm shunt (40do)	70d	Death
33	1.5	22	HLHS	Stent on Coarctation (41 do), Hybrid (56 do)	111d	Death
34	1.9	31	HLHS	Norwood (63 do)	63d	Death
35	1.8	13	Tricuspid atresia	Norwood (33 do)	21m	Death
36	2.5	2	Tricuspid atreisa, PA	Lost to follow-up		

Pt	Wt (kg)	Age (day)	Diagnoses	Intervention Type	Intervention Site	Intervention Balloon / Stent (mm)	Surgery	Last follow-up Age	Last follow-up Outcome
Other interventions									
37	2.2	58	HLHS, s/p Hybrid, CHARGE	Angioplasty	LIV	2x25	None	63d	Death
				Angioplasty	Coarctation	4x20			
38	2.5	32	HLHS, s/p Norwood	Angioplasty	BTS	4x20	None	37d	Death
	2.5	33	HLHS, s/p Norwood	Stent	mBTS	Vision coronary 3.5x12			
39	1.4	9	Obstructed TAPVR	Stent	Vertical vein	Vision coronary 12x40	Lost to follow-up		
40	2.3	5	TOF, PA, LPA stenosis	Stent	LPA	Vision coronary 4x12	Rastelli (198d)	6y	Alive
41	2.5	23	Cardiomyopathy	Pacemaker	RV	Brad bipolar pacing lead	None	53d	Death

Balloon atrial septostomy and atrial septal dilation: 23 interventions were performed in 20 patients. Three patients (Pt 18, 27, 28) had repeat balloon atrial septostomy. Pt 10 underwent balloon pulmonary vavuloplasty and Pt 18 underwent balloon aortic valvuloplasty at the same catheterization. Other interventions: Six interventions were performed in five patients. One patient (Pt 38) underwent two interventions such as angioplasty and stent placement.

served as a palliative procedure (89%) and was curative in small number of patients with isolated valvar PS and AS (11%). The long-term mortality for the entire cohort was 36%.

BPV has an excellent long-term follow-up outcome in children [9]. However, there is scanty follow-up data of BPV in LBW infants. Simpson et al. reported the follow-up data of BPV in eight infants weighing ≤ 2.5 kg with isolated valvar PS [6]. In a median follow-up of 31 months (range 1 month to 10 years), the re-intervention rate was 71% (5/7) at 1 year. Authors concluded that BPV should be regarded as an initial palliation because most patients require additional dilation as they grow. In contrast, our study showed 67% (4/6) patients with isolated valvar PS did not require re-intervention at longer median follow-up of 6 years (Table I). Our data may suggest BPV can be a definitive therapy even in LBW infants with isolated

TABLE III. Significant Adverse Events in Infants Weighing < 2.5 kg

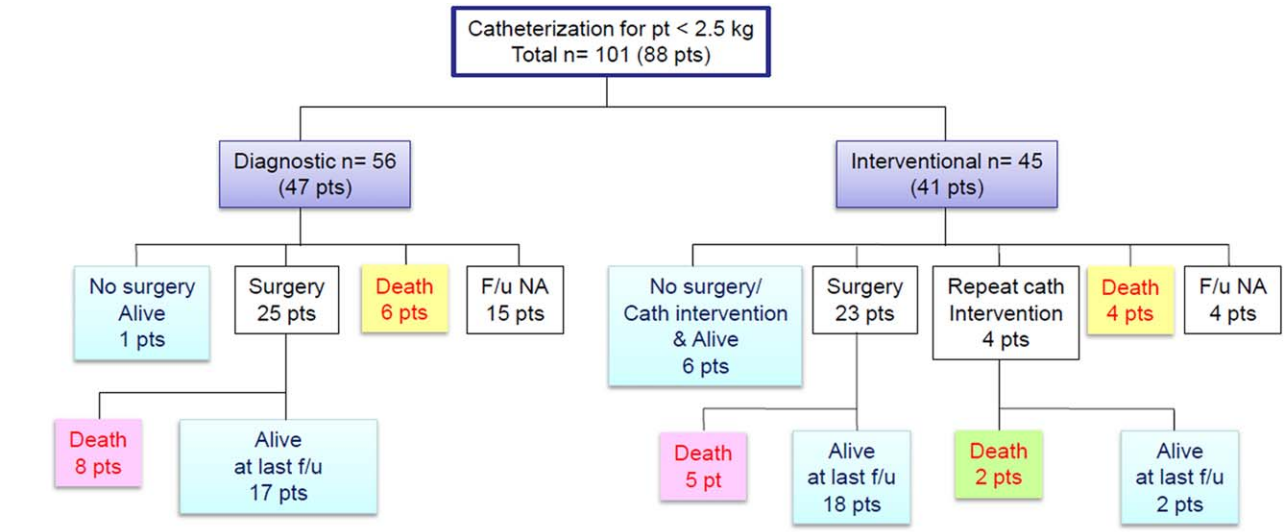
		Comment	Total ($n = 101$)	Diagnostic Group ($n = 56$)	Interventional Group ($n = 45$)	P value
Death			0	0	0	NS
CPR			3	0	3	
Arrhythmia		SVT treated with adenosine	2	1	1	
		SVT and transient heart block	1	1	0	
Vascular	Arterial	Lost femoral pulses treated with heparin	3	2	1	
	Venous	Occlusion / damage to IVC	2	1	1	
		Bilateral femoral vein occlusion	1	0	1	
Respiratory		Apnea requiring intubation	1	1	0	
Total			13 (13%)	6/55 (11%)	7/46 (16%)	0.56

CPR, cardiopulmonary resuscitation; IVC, inferior vena cava; SVT, supraventricular tachycardia. Interventional group: CPR (Pt 7, 13 and 39), arrhythmia (Pt 31), vascular arterial (Pt 1), vascular venous (Pt 5 and 33).

valvar PS. BAV is effective for relief of congenital AS. Infants who underwent BAV within 30 days of life had significantly higher hazard (hazard ratio 5.3) for repeat balloon dilation, though follow-up data of this procedure in LBW infants is limited [10]. Sutton et al. reported four patients with BAV [8]. One patient did not require re-intervention and had mild aortic regurgitation and stenosis at 4.5-year-old. In our study, of the two patients with isolated AS, one patient did not require repeat intervention or surgery at 6 years of age. Regarding other interventions, BAS and dilation were palliative with subsequent shunt or arterial switch procedure. In our study, 94% (17/18) underwent subsequent definitive or palliative surgery; only one patient (6%) died prior to surgery. Our results are comparable to results from previous studies [7]. Diagnostic procedures were predominantly performed to evaluate anatomy and were helpful in evaluating pulmonary arterial and venous anatomy, thus playing a crucial role in planning future surgical or palliative treatment.

Previous studies have consistently reported a higher prevalence of CHD in preterm infants and still birth, suggesting potential causal relationship, though its exact cause and effect is poorly understood [1,11]. Although increased prenatal detection of CHD potentially leads to induction of labor and elective cesarean section before term, premature delivery is generally not recommended [11]. More recently, Laas et al. showed a significantly higher risk (odds ratio 2.0) of preterm birth in infants with CHD in a large population based study, because of an increase in spontaneous preterm birth with no evidence of an increase in induced labor or cesarean delivery before labor [12]. Our finding of twice higher SAE rate in infants weighing less than 2.5 kg as compared to that in infants weighing 2.5–3.5 kg is not surprising, as several studies have shown significantly higher early morbidity and mortality in premature infants [4,13]. The precise mechanisms predisposing LBW infants to adverse outcomes are not known. However, postulated explanations include physiologic role of nitric oxide and surfactant production, and fetal lung fluid clearance in the final weeks of pregnancy in postnatal lung function. Incomplete maturation of lungs, central nervous system and other organ system in LBW infants with CHD are additional factors [3,13]. The vascular complications were significantly higher in LBW infants in our cohort, likely because of a smaller vessel caliber, variable use of heparin and its anticoagulant effects in neonates. The arterial complications were likely under-represented in infants weighing < 2.5 kg as left heart intervention were less frequent. Interestingly, the respiratory complications were not significantly different. This could be because of elective use of endotracheal intubation in most cases of LBW infants.

Several studies have reported that the complications related to cardiac catheterization in infants weighing ≤ 2.5 kg ranged from 26% to 56% [4–7]. Complications were more often seen in interventional than in diagnostic catheterization. The most common complications during interventions were arrhythmia, vascular injury and major complications included respiratory deterioration and death [5–8]. In our study, the SAE rates between diagnostic and interventional catheterizations were not statistically different (11% vs. 16%), because of low overall SAE rate and a limited sample size. There was no catheterization-related mortality in our study. Infants with LBW because of premature lungs, lower lung compliance, and edematous lungs are at increased risk of respiratory compromise [7]. Not surprisingly, respiratory issues were responsible for the majority of complications requiring cardiopulmonary resuscitation. Elective endotracheal intubation to protect and maintain stable airway as well as frequent procedural checks to avoid accidental extubation should be a routine practice. Monitoring



Pt	Diagnosis	Surgery / Intervention	Cause of death
1	TOF/PA	BTS, PDA ligation	Died on HP arrival
2	DORV, d-malposition	LMBTS, PA angiopl	Child abuse
3	PA/VSD, IUGR, Chromsome 9 duplication	RMBTS, PA angiopl	Persistent hypoxia
4	Tricuspid Atresia, TAPVR, heterotaxy	LMBTS, TAPVR repair	RF / Bronchiolitis
5	PA/VSD, PAPVR	Surgery	Sepsis
6	TGA/VSD	Surgery	NA
7	HLHS	DKS	Coaguloplathy
8	PAPVR, VSD	PAPVR, VSD repair	Sepsis
9	IAA, massive hemangioma	None	RF / RSV pneumonia
10	PA/IVS, MAPCA, DiGeorge	None	Died at home
11	TOF/PA, MAPCA	None	Renal failure
12	DORV, unbalanced AVCD, urethral atresia	None	Renal failure
13	CoA, PDA, IUGR	None	NA
14	PA/VSD, MAPCA, DiGeorge	None	Died on HP arrival

Pt	Diagnosis	Surgery / Intervention	Cause of death
1	Tricuspid atresia	DKS, BTS	RF / Pneumonia
2	HLHS	Norwood	Persistent hypoxia
3	DORV, TGA, IAA	Jatene, IAA repair	RF / Pneumonia
4	PA/IVS, MAPCA	Unifocalization, AP shunt	NA
5	Complicated PS, VSD Trisomy 10, Monosomy 5	Surgery	RF / Pneumonia
6	HLHS s/p Hybrid	CoA stent, ASD stent	RF / Influ B pneumonia
7	HLHS s/p Hybrid	Re-stent on PDA stent	NEC
8	Complicated PS, TOF, Trisomy 18	None	Palliative care
9	TGA, IUGR	None	NEC
10	HLHS, s/p Hybrid, CHARGE syndrome	None	Sepsis
11	Cardiomyopathy, fetal SVT, ECMO	None	Heart failure

Fig. 2. Long-term outcome of 88 patients < 2.5 kg (101 catheterizations). ASD, atrial septal defect; AVCD, atrioventricular canal defect; BTS, Blalock-Taussig shunt; CoA, coarctation of aorta; DKS, Damus-Kaye-Stansel procedure; DORV, double outlet right ventricle; ECMO, extracorporeal membrane oxygenation; f/u, follow up; HLHS, hypoplastic left heart syndrome; HP, hospital; IAA, interrupted aortic arch; influ B, influenza virus type B; IUGR, intrauterine growth retardation; IVS, intact ventricular septum; LMBTS, left modified Blalock-Taussig shunt; MAPCA, major aortopulmonary collateral arteries; NA, not available; NEC, necrotizing enterocolitis; PA, pulmonary atresia; PA angiopl, pulmonary artery angioplasty; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus, PS, pulmonary stenosis; RF, respiratory failure; RSV, respiratory syncytial virus; SVT, supraventricular tachycardia; TOF, Tetralogy of Fallot; VSD, ventricular septal defect; TGA, transposition of great arteries. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

airway during the procedure is performed by either the catheterization laboratory nurse or anesthesia team based on primary personnel responsible for sedation and airway management. Vascular complications were similar to previously reported studies. Interestingly, we found two cases of IVC thrombosis and one case of bilateral femoral vein thrombosis following catheterization and these were noted in subsequent catheterization. Among six infants weighing < 2.5 kg with vascular complications, five (83%) had no heparin use during the catheterization. Optimization of anticoagulation may be one of the preventive measures to reduce the risk of vascular complications in LBW infants undergoing catheterization. Screening with preprocedural head ultrasound, coagulation profile prior to use of standard procedural heparin dose with regular ACT checks may be prudent even in infants undergoing diagnostic or interventional right heart catheterization. Moreover, anticoagulant effect of heparin can be impaired in neonates because of much lower level of endogenous anticoagulant antithrombin [14]. Recently, a newer direct thrombin inhibitor, Bibalirubin, was studied in pediatric patients (including neonates) undergoing catheterizations [15]. Bibalirubin had

shorter and more predictable half-life with no increased risk of bleeding complications or other safety concerns. Therefore, Bibalirubin may be a potential alternative to heparin to reduce the risk of vascular complications in LBW infants.

Various factors for early mortality in LBW infants have been extensively reported and included low Apgar scores <5, prolonged mechanical ventilation, greater surgical complexity, prolonged cardiopulmonary bypass time, increased risk of infection, small size of cardiovascular structures with immaturity of myocyte calcium handling proteins, need for postoperative cardiopulmonary resuscitation, use of ECMO, associated major congenital anomalies, diagnosis of hypoplastic left heart syndrome and its variants [3,4]. In our heterogeneous group of LBW infants, the primary focus was catheterization-based intervention and its outcome. Thus, assessing factors for early and late surgical mortality was beyond the scope of this study. Following catheterization, most of the patients underwent further surgical palliative or complete repair. The early mortality rate in LBW/premature infants is significantly higher than that in term infants. Costello et al. reported a higher mortality rate in premature infants in a large cohort of 971 patients with CHD (3% for 38–39 weeks gestation, 7% for 37–38 weeks, and 32% for <34 weeks gestation). In addition, LBW infants were associated with greater rate of fetal compromise, CHD, and chromosomal anomalies. [13]. The primary strategies employed to reduce mortality in LBW infants are (1) early surgical approach that offers benefits of avoiding hemodynamic effects and secondary damage to end organs and (2) delayed surgery to allow weight gain and to attain mature gestational age. The outcomes in either strategy are not significantly different. Cheng et al. reported a high in-hospital mortality of 18% and 5-year mortality of 23% in 174 premature infants with critical CHD who underwent cardiac interventions (including surgery and catheter intervention) during the first month of life [4]. In contrast, our institutional strategy for LBW infants is delayed surgical approach assisted by medical management and catheterization-based intervention prior to definitive or staged surgical palliative approach. We report early mortality of 19% and overall mortality of 36% with a median follow-up of 3 years in our cohort. This is similar to other studies from institutions advocating early repair with early mortality ranging from 15% to 42% [3,4,16,17]. Our low catheterization-related complication rate and acceptable overall mortality augur well to delayed surgical approach employed by our and other institutions in treating LBW infants with complex CHD.

Our study was conducted retrospectively and could underestimate the SAE rates. The late complication rate of vessel injury is unknown, because of no routine imaging study of access vessels after the catheterization. However, the vessel injuries found in the following catheterization were included in our study. Furthermore, all infants within 48 hours of procedure with adverse events were routinely reported and evaluated in neonatal intensive care unit, thus eliminating under-reporting of any procedure related SAE. Our data regarding long-term survival and mortality may be higher than reported as we had follow-up information available only in 78% of patients. Nevertheless, this study highlights a large cohort of LBW infants undergoing catheterization in a single center with minimal complications compared to previous studies (during similar time frame) and no catheterization-related mortality.

CONCLUSIONS

Interventional catheterization is technically feasible with relatively low morbidity and mortality in high risk infants weighing less than 2.5 kg. In most infants catheterization primarily serves as a palliative procedure to stabilize infants for definitive treatment. However, balloon valvuloplasty may be an effective treatment for small group of isolated valvar pulmonary stenosis. The long-term mortality in these high-risk infants remains high.

REFERENCES

1. Rosenthal GL, Wilson PD, Permutt T, Boughman JA, Ferencz C. Birth weight and cardiovascular malformations: A population-based study. The Baltimore-Washington Infant Study. Am J Epidemiol 1991;133:1273–1281.
2. MacDorman MF, Mathews TJ. The challenge of infant mortality: Have we reached a plateau? Public Health Rep 2009;124: 670–681.
3. Ades AM, Dominguez TE, Nicolson SC, Gaynor JW, Spray TL, Wernovsky G, Tabbutt S. Morbidity and mortality after surgery for congenital cardiac disease in the infant born with low weight. Cardiol Young 2010;20:8–17.
4. Cheng HH, Almodovar MC, Laussen PC, Wypij D, Polito A, Brown DW, Emani SM, Pigula FA, Allan CK, Costello JM. Outcomes and risk factors for mortality in premature neonates with critical congenital heart disease. Pediatr Cardiol 2011;32: 1139–1146.
5. Rhodes JF, Asnes JD, Blaufox AD, Sommer RJ. Impact of low body weight on frequency of pediatric cardiac catheterization complications. Am J Cardiol 2000;86:1275–1278, A9.
6. Simpson JM, Moore P, Teitel DF. Cardiac catheterization of low birth weight infants. Am J Cardiol 2001;87:1372–1377.
7. McMahon CJ, Price JF, Salerno JC, El-Said H, Taylor M, Vargo TA, Nihill MR. Cardiac catheterisation in infants weighing less than 2500 grams. Cardiol Young 2003;13:117–122.

8. Sutton N, Lock JE, Geggel RL. Cardiac catheterization in infants weighing less than 1,500 grams. Catheter Cardiovasc Interv 2006;68:948–956.
9. Rao PS, Galal O, Patnana M, Buck SH, Wilson AD. Results of three to 10 year follow up of balloon dilatation of the pulmonary valve. Heart 1998;80:591–595.
10. Brown DW, Dipilato AE, Chong EC, Lock JE, McElhinney DB. Aortic valve reinterventions after balloon aortic valvuloplasty for congenital aortic stenosis intermediate and late follow-up. J Am Coll Cardiol 2010;56:1740–1749.
11. Tanner K, Sabrine N, Wren C. Cardiovascular malformations among preterm infants. Pediatrics 2005;116:e833–e838.
12. Laas E, Lelong N, Thieulin AC, Houyel L, Bonnet D, Ancel PY, Kayem G, Goffinet F, Khoshnood B; on behalf of the EPICARD Study Group. Preterm birth and congenital heart defects: A population-based study. Pediatrics 2012;130:e829–e837.
13. Costello JM, Polito A, Brown DW, McElrath TF, Graham DA, Thiagarajan RR, Bacha EA, Allan CK, Cohen JN, Laussen PC. Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. Pediatrics 2010;126:277–284.
14. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:645S–687S.
15. Forbes TJ, Hijazi ZM, Young G, Ringewald JM, Aquino PM, Vincent RN, Qureshi AM, Rome JJ, Rhodes JF Jr, Jones TK, Moskowitz WB, Holzer RJ, Zamora R. Pediatric catheterization laboratory anticoagulation with bivalirudin. Catheter Cardiovasc Interv 2011;77:671–679.
16. Oppido G, Pace Napoleone C, Formigari R, Gabbieri D, Pacini D, Frascaroli G, Gargiulo G. Outcome of cardiac surgery in low birth weight and premature infants. Eur J Cardiothorac Surg 2004;26:44–53.
17. Reddy VM. Cardiac surgery for premature and low birth weight neonates. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2001;4:271–276.