Outcomes of cardiac surgery in patients weighing <2.5 kg: Affect of patient-dependent and -independent variables

David Kalfa, MD, PhD,[a] Ganga Krishnamurthy, MD,[b] Jennifer Duchon, MD,[b] Marc Najjar, MD,[a] Stéphanie Levasseur, MD,[c] Paul Chai, MD,[a] Jonathan Chen, MD,[d] Jan Quaegebeur, MD, PhD,[a] and Emile Bacha, MD[a]

Objective: A recent Society of Thoracic Surgeons database study showed that low weight (<2.5 kg) at surgery was associated with high operative mortality (16%). We sought to assess the outcomes after cardiac repair in patients weighing <2.5 kg versus 2.5 to 4.5 kg in an institution with a dedicated neonatal cardiac program and to determine the potential role played by prematurity, the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) risk categories, uni/biventricular pathway, and surgical timing.

Methods: We analyzed the outcomes (hospital mortality, early reintervention, postoperative length of stay, mortality [at the last follow-up point]) in patients weighing <2.5 kg at surgery (n = 146; group 1) and 2.5 to 4.5 kg (n = 622; group 2), who had undergone open or closed cardiac repairs from January 2006 to December 2012 at our institution. The statistical analysis was stratified by prematurity, STAT risk category, uni/biventricular pathway, and usual versus delayed surgical timing. Univariate versus multivariate risk analysis was performed. The mean follow-up was 21.6 ± 25.6 months.

Results: Hospital mortality in group 1 was 10.9% (n = 16) versus 4.8% (n = 30) in group 2 ($P = .007$). The postoperative length of stay and early unplanned reintervention rate were similar between the 2 groups. Late mortality in group 1 was 0.7% (n = 1). In group 1, early outcomes were independent of the STAT risk category, uni/biventricular pathway, or surgical timing compared with group 2. A lower gestational age at birth was an independent risk factor for early mortality in group 1.

Conclusions: A dedicated multidisciplinary neonatal cardiac program can yield good outcomes for neonates and infants weighing <2.5 kg independently of the STAT risk category and uni/biventricular pathway. A lower gestational age at birth was an independent risk factor for hospital mortality. (J Thorac Cardiovasc Surg 2014;148:2499-506)

See related commentary on pages 2506-7.

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Despite improvements in the outcomes in neonatal cardiac surgery during the past 20 years, low weight remains a risk factor for increased mortality in neonates and infants undergoing cardiac surgery.[1] A Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database study, with 32 participating centers, recently demonstrated that the average operative mortality rate in patients with a low weight (≤2.5 kg) at surgery was as high as 16%.[2] Moreover, the risk factors for mortality and reintervention in that specific population are still controversial.[3-10] To our knowledge, the potential role played by the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) risk categories, the uni/biventricular pathway, timing of surgery, and gestational age were never investigated in a study directly comparing 2 groups of patients (those weighing ≤2.5 kg and those weighing >2.5 kg). Thus, the objectives of our study were to (1) assess the early and mid-term outcomes of cardiac repair in patients weighing ≤2.5 kg in an institution with a dedicated neonatal cardiac program; (2) compare these results with those of patients weighing 2.5 to 4.5 kg undergoing surgery at the same institution; (3) determine the potential role played by gestational age, STAT risk category, uni/biventricular pathway, and timing of surgery; and (4) perform univariate and multivariate risk analysis of the group weighing ≤2.5 kg.

METHODS

The present retrospective single-center study included patients who had undergone open or closed cardiac surgery at the New York-Presbyterian Morgan

From the Divisions of Pediatric Cardiac Surgery,[a] Neonatology,[b] and Pediatric Cardiology,[c] New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, NY; and the Division of Pediatric Cardiac Surgery,[d] Seattle Children's Hospital, University of Washington, Seattle, Wash.

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Address for reprints: Emile Bacha, MD, Division of Pediatric Cardiac Surgery, New-York Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, 3959 Broadway, New York, NY 10032 (E-mail: eb2709@cumc.columbia.edu).

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Abbreviations and Acronyms
ANOVA = analysis of variance
STAT = Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery
STS = Society of Thoracic Surgeons
TOF = tetralogy of Fallot

Stanley Children's Hospital, Columbia University Medical Center, from January 2006 to December 2012 with a weight of ≤2.5 kg at surgery (group 1) or 2.5 to 4.5 kg (group 2). The patients who underwent ductus arteriosus closure alone were not included in the present study. The perioperative data were retrospectively collected by reviewing the hospital records and the computerized database of our department. Follow-up data were obtained from the institution outpatient records and the same computerized database.

The dedicated neonatal cardiac program offers care to neonates or young infants with congenital heart disease from birth to discharge. A dedicated medical and nursing team staff this program and included members from the neonatal intensive care, pediatric cardiology, and pediatric cardiac surgery divisions. The practitioners on this team had either received advanced training in pediatric cardiac intensive care and/or had an advanced understanding and were skilled in the management of newborn infants with congenital heart disease. Dedicated neonatal cardiac intensive care nurses and neonatal nurse practitioners, neonatal respiratory therapists, and neonatal nutritionists and feeding specialists staffed the neonatal cardiac intensive care unit. Patients who were born at our institution or transferred from outside medical centers with known or suspected congenital heart disease were admitted to the neonatal cardiac intensive care unit of the neonatal intensive care unit. Although no clear cut restrictions to admission to the neonatal cardiac intensive care unit were in place, infants >6 to 8 weeks of age at transfer or admission were preferably admitted to our pediatric cardiac intensive care unit.

The STAT risk categories, uni/biventricular pathway, and timing of surgery were assigned for each patient included in the present study. The STAT risk categories were determined from the definition of the categories established by O'Brien and colleagues.[11] The surgical pathway was defined as "univentricular" (Norwood procedure, aortopulmonary shunt, pulmonary artery band, and/or atrial septectomy performed for single ventricle disease), "biventricular" (primary biventricular complete repair), or "palliation toward biventricular" (systemic-pulmonary shunt, pulmonary artery band, unifocalization, and/or transannular patch as a first step before biventricular repair). The timing of surgery was defined as "usual" (determined from usual divisional management paradigms for infants of normal weight) or "delayed" (intentional delay of early intervention or unusual choice of a palliative approach to permit growth or maturation), as previously described by Hickey and colleagues.[12] This adjudication of the surgical timing was determined from an accurate and precise retrospective medical record review by the senior coauthors (D.K., E.B.). The mean age at surgery for patients with the usual timing of surgery was 10.9 ± 11.9 days versus 50.6 ± 36 days for those with delayed surgery.

The primary endpoint was mortality occurring before hospital discharge or within 30 days postoperatively. The secondary endpoints were the postoperative hospital length of stay (LOS), unplanned early reintervention (during the same hospital stay), and late mortality. The institutional review board of Columbia University Medical Center approved the study.

Population

A total of 146 and 622 patients were included in groups 1 and 2, respectively. The demographic and surgical characteristics, cardiac diagnoses, STAT categories, surgical pathway, and timing of surgery of both groups are listed in Table 1. Of the patients in group 1, 70% (n = 102) had a STAT 4 or 5 risk category, 63% (n = 92) a biventricular pathway, and 18.5% (n = 27) delayed timing. Compared with group 2, group 1 was characterized by a statistically significant lower male/female ratio ($P = .01$), older age at surgery ($P < .001$), more patients with tetralogy of Fallot (TOF) ($P = .006$), and more with an aortopulmonary window ($P = .02$) but fewer with simple transposition of the great arteries ($P = .04$), more with STAT 2 category ($P = .01$), and a shorter bypass time ($P = .01$). Single ventricles, right-side heart lesions, aortic arch lesions, and transposition of the great arteries were the most frequent group of diseases in both groups. Patients in group 1 had extracardiac malformations and a genetic syndrome in 18.4% and 13% of cases, respectively. The mean gestational age at birth for patients in group 1 was 35.5 ± 2.8 weeks. In group 1, 56% of the patients (n = 82) were premature (<37 weeks) and 42% (n = 61) had a gestational age of <36 weeks. Also, 42% were small for their gestational age (defined as <10th percentile). In group 1, 41% (n = 33) of the STAT 4 patients had a gestational age of <36 weeks compared with 25% (n = 6) of the STAT 5 patients ($P = .15$). Of the patients who underwent a univentricular pathway in group 1, 22% (n = 9) had a gestational age of <36 weeks versus 48% (n = 44) of those with a biventricular pathway ($P = .007$) and 61% (n = 8) of those with palliation toward biventricular repair ($P = .014$).

The frequencies of the main procedures in groups 1 and 2 are listed in Table E1. The 4 most frequent procedures performed in group 1 were the Norwood procedure (n = 25; 17%), the arterial switch operation (n = 13; 8.9%), primary repair of TOF (n = 12; 8.2%), and shunt palliation or unifocalization for TOF or pulmonary atresia with a ventricular septal defect (n = 12; 8.2%). The latter procedure was performed more frequently in group 1 (8.2%; n = 12) than in group 2 (3.2%; n = 20; $P = .01$). The frequency of all other procedures was not significantly different between the 2 groups. Of the patients who underwent a Norwood procedure in group 1, 20% (n = 5) had a gestational age of <36 weeks versus 62% (n = 5) of those who underwent hypoplastic aortic arch repair ($P = .036$).

Statistical Analysis

Descriptive statistics were performed and stratified by weight of ≤2.5 kg versus >2.5 kg. Bivariate testing by weight category for demographic and surgical characteristics and for the outcomes of hospital mortality, postoperative hospital LOS, early unplanned reintervention, and late mortality was performed for categorical variables using Fisher's exact test or the chi-square test and for continuous variables using the Student *t* test, the Wilcoxon rank sum test, analysis of variance (ANOVA), or the Kruskal-Wallis test. Multiple comparisons were explored using Tukey's test. Trends for ordinal independent variables were performed using *P* for trend (ANOVA) or the Cochran-Armitage test for trend. Comparisons between the endpoints and demographic and surgical characteristics between the weight categories were performed using the Cochran Mantel-Haenszel or 2-way ANOVA, first testing for interaction with the Breslow-Day test or by creating interaction terms in 2-way ANOVA. The statistical analysis was stratified by the STAT risk categories, surgical pathway, and timing of surgery.

A risk analysis was performed for the endpoints of early mortality and early unplanned reintervention in group 1. Univariate analysis was performed for the categorical variables using Fischer's exact test or the chi-square test and for continuous variables using the Student *t* test or Mann-Whitney *U* test. Multivariate analysis was performed using a logistic regression model to estimate the risk factors for early mortality and early unplanned reintervention. Variables were included into the model by backward elimination if $P < .05$. The adjustment factors for multivariate analysis were the surgeon, STAT score, procedure type (uni/biventricular), and gestational age at birth. Postoperative complications were defined as ≥1 of the following postoperative major events: cardiac arrest, extracorporeal membrane oxygenation, arrhythmia, atrioventricular block requiring a pacemaker, diaphragm paralysis, atelectasis, pleural effusion requiring thoracocentesis, respiratory failure, seizure, cerebrovascular event, renal failure requiring dialysis, necrotizing enterocolitis, mediastinitis, or any septic syndrome. Statistical Analysis Systems, version 9.3 (SAS Institute, Cary, NC), was used for data analysis.

TABLE 1. Patient characteristics and overall outcomes

Variable	Group 1 (<2.5 kg; n = 146)	Group 2 (2.5-4.5 kg; n = 622)	*P* value
Male sex	71 (49)	377 (60.7)	.01*
Birth weight (kg)	2.1 ± 0.4	3.1 ± 0.5	NA†
Weight at surgery (kg)			<.001*
Mean ± SD	2.2 ± 0.3	3.2 ± 0.4	
Range	1.1-2.50	2.51-4.4	
Age at surgery (d)			<.001*
Mean ± SD	18.2 ± 24.2	10.1 ± 15.3	
Range	1-193	0-215	
Proportion of neonates (age, <31 d)	112/146 (76)	592/622 (95)	
Cardiac diagnoses			
Single ventricle	38 (26.1)	190 (30.5)	.27
HLHS	21 (14.4)	126 (20.2)	.13
Tricuspid atresia	6 (4.1)	18 (2.9)	.42
Double-inlet left ventricle	5 (3.4)	23 (3.7)	1
Unbalanced AVSD	3 (2.1)	11 (1.8)	.72
Heterotaxy syndromes	2 (1.4)	11 (1.8)	.75
Single ventricle, NOS	1 (0.7)	1 (0.6)	1
Right heart lesions	30 (20.5)	71 (11.4)	.006*
Tetralogy of Fallot	17 (11.6)	30 (4.8)	.006*
Pulmonary atresia, VSD	7 (4.8)	20 (3.2)	.61
Pulmonary atresia, no VSD	4 (2.7)	18 (2.9)	.57
Pulmonary stenosis	2 (1.4)	3 (0.5)	.32
Aortic arch lesions	22 (15)	112 (18)	.78
Interrupted aortic arch	6 (4.1)	23 (3.7)	.18
Coarctation of aorta + hypoplastic arch	8 (5.5)	57 (9.2)	.24
Coarctation of aorta + VSD	8 (5.5)	32 (5.1)	.63
TGA	22 (15)	134 (21.5)	.13
TGA, intact ventricular septum	13 (8.9)	85 (13.7)	.045*
TGA, VSD	8 (5.5)	33 (5.3)	.83
TGA, VSD, aortic arch hypoplasia	1 (0.7)	13 (2.1)	.33
ccTGA	0	3 (0.5)	1
VSD	9 (6.2)	19 (3)	.15
Truncus arteriosus	8 (5.5)	14 (2.2)	.06*
TAPVR	9 (6.2)	47 (7.6)	.37
AVSD	2 (1.4)	4 (0.6)	.41
Aortopulmonary window	4 (2.7)	1 (0.16)	.02*
Ebstein anomaly	1 (0.7)	1 (0.16)	.09
Double outlet right ventricle	0	16 (2.6)	.07
Cardiac tumor	1 (0.7)	5 (0.8)	1
Aortic stenosis	0	6 (1)	NA
Coronary anomalies	0	2 (0.3)	1
Pathway			
Univentricular surgery	41 (28.1)	208 (33.9)	.2
Palliation toward biventricular repair	13 (8.9)	48 (7.7)	.73
Biventricular repair	92 (63)	365 (58.6)	.37
Timing of surgery			NA
Usual	119 (81.5)	622 (100)	
Delayed	27 (18.5)	0 (0)	
STAT risk category			
1	10 (6.8)	23 (3.7)	.11
2	16 (11)	32 (5.1)	.013*
3	18 (12.3)	115 (18.5)	.09
4	78 (53.4)	308 (49.5)	.4
5	24 (16.4)	144 (23.1)	.095
Open heart cases	138 (94.5)	569 (91.5)	.3
Bypass time (min)	114 ± 46	123 ± 44	.011*
Crossclamp time (min)	52 ± 22	57 ± 30	.11
Early mortality	16 (10.9)	30 (4.8)	.0069
Postoperative LOS (d)	20.3 ± 24.5	19.6 ± 24.7	.46
Early reintervention	9 (6.2)	31 (4.9)	.55
Mortality at last follow-up visit	1 (0.7)	18 (3)	.15

Data presented as mean ± SD or n (%), unless noted otherwise. *SD*, Standard deviation; *HLHS*, hypoplastic left heart syndrome; *AVSD*, atrioventricular septal defect; *NOS*, not otherwise specified; *VSD*, ventricular septal defect; *TGA*, transposition of the great arteries; *ccTGA*, congenitally corrected TGA; *TAPVR*, total anomalous pulmonary venous return; *LOS*, length of stay; *NA*, not applicable; *STAT*, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery. *Statistically significant. †Missing birth weight data in group 2 made the comparison not methodologically acceptable.

RESULTS

The overall outcomes are listed in Table 1. Hospital mortality was significantly greater in group 1 than in group 2 (10.9% vs 4.8%; $P = .0069$). The cause of hospital death in group 1 was related to heart failure in 12, respiratory failure in 2, and sepsis in 2. The postoperative hospital LOS, early unplanned reintervention rate, and mortality at the last follow-up point were similar between the 2 groups. Late mortality in patients weighing <2.5 kg was 0.7% (n = 1).

Outcomes Stratified by Gestational Age, STAT Score, Surgical Pathway, and Surgical Timing

The outcomes in patients weighing <2.5 kg, stratified by gestational age, STAT score, surgical pathway, and surgical timing are presented in Table 2. In group 1, each outcome was independent of the STAT risk category, uni/biventricular pathway, or timing of surgery. Hospital mortality was 8.3% (n = 2) for those in the STAT 5 category and 12.2% (n = 5) for the patients in the univentricular pathway. Hospital mortality was 9.2% (n = 11) when the surgical timing was usual versus 18.5% (n = 5) when surgery was delayed to allow growth and maturation of the patient ($P = .18$). Hospital mortality was significantly associated with a gestational age of <36 weeks (18% vs 5.8%; $P = .03$; Table 2).

The outcomes of the patients weighing >2.5 kg, stratified by STAT score and surgical pathway showed that the early mortality rate and postoperative hospital LOS were significantly increased in the higher STAT categories ($P < .001$ and $P = .007$, respectively). Early mortality, postoperative hospital LOS, and early unplanned

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TABLE 2. Outcomes of surgery in patients <2.5 kg stratified by STAT score, uni/biventricular pathway, and surgical timing

STAT risk category	1	2	3	4	5	*P* value
Early mortality	0/10	3/16 (18.7)	1/18 (5.6)	10/78 (12.8)	2/24 (8.3)	.53
Postoperative LOS (d)	17.7 ± 13.8	24.8 ± 27.1	13.5 ± 9	20.6 ± 27.8	22.8 ± 22.6	.68
Early reintervention	0/10	1/16 (6.2)	1/18 (5.6)	6/78 (7.7)	1/24 (4.2)	.93

Surgical pathway	Biventricular	Palliation toward biventricular	Univentricular	*P* value
Early mortality	9/92 (9.8)	2/13 (15.4)	5/41 (12.2)	.8
Postoperative LOS (d)	20.5 ± 26.1	16.2 ± 9.8	21 ± 24.2	.97
Early reintervention	4/92 (4.3)	2/13 (15.4)	3/41 (7.3)	.28

Surgical timing	Usual	Delayed	*P* value
Early mortality	11/119 (9.2)	5/27 (18.5)	.18
Postoperative LOS (d)	20.8 ± 26	18.2 ± 16.5	.85
Early reintervention	7/119 (5.9)	2/27 (7.4)	.67

Gestational age (wk)	<36	≥36	*P* value
Early mortality	11/61 (18)	5/85 (5.8)	.03*
Postoperative LOS (d)	24.2 ± 31.6	18.7 ± 19.8	.21
Early reintervention	1/61 (1.6)	8/85 (10.3)	.08

Data presented as n (%) or mean ± standard deviation. *LOS*, Length of stay; *STAT*, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery. *Statistically significant.

reintervention were also significantly more frequent with the univentricular pathway than with the biventricular pathway ($P < .001$ for each outcome). In group 2, hospital mortality was 10.4% (n = 15) for those in the STAT 5 category and 9.9% (n = 21) for the patients in the univentricular pathway.

Comparative Analysis of Outcomes Between Groups 1 and 2 by Diagnosis and Procedure Group, STAT Score, and Surgical Pathway

The mortality rates stratified by diagnosis and procedure group between groups 1 and 2 are listed in Table 3. The mortality rate was significantly greater in group 1 after aortic arch repair (for a hypoplastic arch) than in group 2 (25% vs 0%; $P = .02$). Also, a trend was seen for greater mortality in group 1 than in group 2 after total anomalous pulmonary venous return repair (22.2% vs 4.3%; $P = .15$), aortopulmonary shunt for TOF (16.7% vs 0%; $P = .16$), and arterial switch associated with ventricular septal defect closure (12.5% vs 0%; $P = .21$). Mortality was similar after the Norwood procedure (8% in group 1 vs 10.6% in group 2; $P = 1.00$) or any palliative procedure for a single ventricle. No death occurred in patients weighing <2.5 kg after the arterial switch operation (0 of 13), interrupted aortic arch repair (0 of 6), truncus arteriosus repair (0 of 7), and pulmonary stenosis (0 of 2).

TABLE 3. Comparative analysis of mortality rates stratified by diagnosis and procedure for both groups

Diagnosis/procedure	Mortality rate			*P* value
	Overall	<2.5 kg	2.5-4.5 kg	
Single ventricle/Norwood	10.2 (17/166)	8 (2/25)	10.6 (15/141)	1.00
Single ventricle/conduit or shunt	11 (5/45)	22.2 (2/9)	8.3 (3/36)	.30
Single ventricle/PA band	6.7 (1/15)	0 (0/3)	8.3 (1/12)	1.00
TGA, IVS/ASO	1 (1/98)	0 (0/13)	1.2 (1/85)	1.00
TGA, VSD/ASO + VSD closure	2.4 (1/41)	12.5 (1/8)	0 (0/33)	.21
TAPVR/repair	7.1 (4/56)	22.2 (2/9)	4.3 (2/47)	.15
Coarctation hypoplastic arch/aortic arch repair through sternotomy	3 (2/65)	25 (2/8)	0 (0/57)	.02*
Coarctation, VSD/aortic arch + VSD repair	2.5 (1/40)	12.5 (1/8)	0 (0/32)	.22
Interrupted aortic arch/repair	3.6 (1/28)	0 (0/6)	4.3 (1/23)	1.00
Truncus arteriosus/repair	4.8 (1/21)	0 (0/7)	7.1 (1/14)	1.00
TOF/primary repair	4.8 (2/42)	8.3 (1/12)	3.3 (1/30)	.51
TOF/shunt palliation	6.2 (2/32)	16.7 (2/12)	0 (0/20)	.16
Aortopulmonary window/repair	20 (1/5)	25 (1/4)	0 (0/1)	1.00
Cardiac tumor/resection	16.7 (1/6)	100 (1/1)	0 (0/5)	.28
Pulmonary stenosis/repair	20 (1/5)	0 (0/2)	33 (1/3)	1.00

Data presented as % (n/n). *PA*, Pulmonary artery; *TGA*, transposition of the great arteries; *IVS*, intact ventricular septum; *ASO*, arterial switch operation; *VSD*, ventricular septal defect; *TAPVR*, total anomalous pulmonary venous return; *TOF*, tetralogy of Fallot. *Statistically significant.

TABLE 4. Comparative analysis of mortality rates stratified by STAT score and surgical pathway

Variable	Mortality rate		Risk ratio (95% CI)	*P* value
	<2.5 kg (n = 146)	2.5-4.5 kg (n = 622)		
STAT risk category				
1	0/10	1/23 (4.3)	NA	NA
2	3/16 (18.8)	1/32 (3.1)	6 (0.67-53.2)	.1
3	1/18 (5.6)	1/115 (0.87)	6.4 (0.42-98)	.25
4	10/78 (12.8)	12/308 (3.9)	3.3 (1.48-7.33)	.005*
5	2/24 (8.3)	15/144 (10.4)	0.8 (0.19-3.3)	1
Surgical pathway				
Biventricular	9/92 (9.8)	8/365 (2.2)	4.4 (1.8-11.2)	.02*
Palliation toward biventricular	2/13 (15.4)	1/48 (2)	7.4 (0.73-75.2)	.11
Univentricular	5/41 (12.2)	21/208 (10)	1.2 (0.5-3.1)	.77

Data presented as n/n (%). *CI*, Confidence interval; *NA*, not applicable; *STAT*, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery. *Statistically significant.

Hospital mortality between groups 1 and 2, stratified by the STAT score and surgical pathway, is listed in Table 4. After such a stratification, the inverse association between infant weight and hospital mortality persisted only in the STAT 4 category subgroup (12.8% in group 1 vs 3.9% in group 2; $P = .005$) and in the biventricular strategy subgroup (9.8% vs 2.2%; $P = .02$).

The postoperative LOS stratified by the surgical strategy was significantly longer in group 1 (20.5 ± 26.1 days) than in group 2 (18.4 ± 16.3 days) after biventricular repair only ($P = .02$). The absence of an association between weight and early unplanned reintervention persisted after stratification by STAT risk category and surgical strategy.

Risk Analysis

The results of the risk analysis for early mortality in patients weighing <2.5 kg are listed in Table 5. The main factors associated with an increased risk of early mortality on univariate analysis included lower gestational age at birth ($P = .013$), the occurrence of postoperative complications ($P < .0001$), cardiac arrest ($P < .0001$), renal failure requiring dialysis ($P = .004$), and atrioventricular block requiring a pacemaker ($P = .03$). Birthweight, the presence of major extracardiac malformations, a genetic syndrome, patient age and weight at surgery, the STAT score, surgical strategy, surgical timing, the surgeon, and the need for an unplanned early reintervention were not associated with an increased risk of hospital mortality. Multivariate analysis demonstrated that lower gestational age at birth (OR, 0.83; 95% confidence interval, 0.69-0.98) was an independent risk factor for early mortality.

The risk analysis for unplanned early reintervention in patients weighing <2.5 kg showed that the occurrence of postoperative complications was an independent risk factor for early reintervention (OR, 18.9; 95% confidence interval, 2.2-160). However, early reintervention in patients weighing <2.5 kg was independent of the surgeon, STAT score, and surgical strategy.

DISCUSSION

Although a weight of <2.5 kg at surgery remains a risk factor for early mortality, a dedicated neonatal cardiac program can yield good early and mid-term outcomes for low-weight neonates or infants independently of the STAT risk category and surgical strategy. A lower gestational age at birth was an independent risk factor for early mortality in neonates or infants weighing <2.5 kg at surgery.

Despite major progress in neonatal cardiac surgery and postoperative care during the past 20 years, a low weight at surgery remains associated with high mortality rates (10%-24%) and high morbidity rates.[3,7,10,13-16] A recent study from Philadelphia, with patient demographics very similar to ours, reported a 24% hospital mortality rate for patients weighing <2.5 kg.[3] Another recent and large report of the STS Congenital Heart Surgery Database analyzed the outcomes of cardiac surgery in >500 infants weighing 1 to 2.5 kg from 32 participating centers.[2] That study demonstrated that this low-weight cohort had significantly greater mortality for specific operations and that lower weight consistently increased the risk of mortality after stratification by risk category.

Our series has confirmed that a weight of <2.5 kg at surgery remains a risk factor for early mortality, with a hospital mortality rate of 10.9%. The rate of early unplanned reintervention was not significantly different between patients weighing <2.5 kg and >2.5 kg, suggesting that the technical surgical factors that might occur in tiny neonates were not the primary cause of the greater mortality seen in the <2.5-kg patients. This was further buttressed because factors such as the STAT risk categories, surgeon, and bypass time also were not related to mortality or early reintervention. Several technically complex procedures such as the arterial switch operation, interrupted aortic arch repair, or truncus arteriosus repair were performed, with no hospital mortality in the <2.5-kg patients. The expertise and the major role played by the surgical and

TABLE 5. Risk analysis for early mortality in patients weighing <2.5 kg

Variable	Survivors (n = 130)	Early death (n = 16)	*P* value
Univariate risk analysis			
Gestational age (continuous) (wk)	35.7 ± 2.8	34 ± 2.7	.013*
Gestational age <36 wk	50 (38.5)	11 (68.8)	.03*
Prematurity (gestational age <37 wk)	70 (53.8)	12 (75)	.12
Birth weight (kg)	2.13 ± 0.43	2.02 ± 0.44	.22
AGA	71 (54.6)	10 (62.5)	.26
SGA	57 (43.8)	5 (31.3)	
LGA	2 (1.5)	1 (6.3)	
Antenatal diagnosis	84 (64.6)	11 (68.8)	1.00
Major extracardiac malformation	25 (19.2)	2 (12.5)	.73
Genetic syndrome	17 (13.1)	3 (18.8)	.46
Surgeon			.072
1	19 (14.6)	2 (12.5)	
2	53 (40.8)	2 (12.5)	
3	25 (19.2)	4 (25)	
4	33 (25.4)	8 (50)	
Age at surgery (d)	7 (1-91)	12.5 (1-64)	.25
Weight at surgery (kg)	2.22 ± 0.25	2.12 ± 0.35	.26
Mean STAT score	3.61 ± 1.1	3.69 ± 0.94	.89
Pathway			
Univentricular	36 (27.7)	5 (31.3)	.77
Palliation toward biventricular	11 (8.5)	2 (12.5)	
Biventricular	83 (63.8)	9 (56.3)	
Timing of surgery			.17
Usual	108 (83.1)	11 (68.8)	
Delayed	22 (16.9)	5 (31.3)	
Bypass	122 (93.8)	16 (100)	.30
Bypass time (min)	110 ± 50	102 ± 48	.67
Postoperative complications	41 (31)	16 (100)	<.0001*
Delayed chest closure	15 (11.5)	5 (31.3)	.047*
Cardiac arrest	4 (3.1)	14 (87.5)	<.0001*
Length of mechanical ventilation (d)	4 (1-32)	12 (1-41)	.09
Arrhythmia	11 (8.5)	7 (43.8)	.001*
AV block requiring pacemaker	1 (0.8)	2 (12.5)	.03*
Pulmonary complications	17 (13.1)	6 (37.5)	.02*
Renal failure requiring dialysis	0	1 (6.3)	.004*
Necrotizing enterocolitis	6 (4.6)	2 (12.5)	.21
Early unplanned reintervention	7 (5.4)	2 (12.5)	.25
Residual lesions at discharge	32 (24.6)	6 (37.5)	.36

Multivariate analysis	*P* value	OR	95% CI
Gestational age (continuous, wk)	.037	0.83	0.69-0.98

Data presented as mean ± standard deviation, n (%), or median (range), unless noted otherwise. Factors of adjustment for multivariate analysis: surgeon, STAT score, procedure type (uni/biventricular), gestational age at birth. *AGA*, Average for gestational age; *SGA*, small for gestational age; *LGA*, large for gestational age; *AV*, atrioventricular; *OR*, odds ratio; *CI*, confidence interval; *STAT*, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery. *Statistically significant.

perfusion teams in the management of cardiopulmonary bypass in low-weight neonates, with significant emphasis on obsessive fluid restriction such as priming volume reduction[17] and a lack of postoperative bleeding to avoid blood product transfusions and the lack of a need for permanent pacemaker implantation, cannot be overemphasized. The greater risk of mortality seems, therefore, to be more related to patient-dependent factors, especially prematurity, such as was demonstrated in the risk analysis. Finally, that major postoperative complications correlated highly with early intervention (OR, 18.9) on multivariate analysis for patients weighing <2.5 kg emphasizes the need to ''get it right the first time'' and avoid being forced to take the patient back for revision or interventional catheterization.

The mortality rate after the Norwood procedure in patients weighing <2.5 kg was low at 8% (n = 2 of 25) at our institution. The mortality rate for low-weight patients undergoing a Norwood procedure in the series based on the STS Congenital Heart Surgery Database was 30%,[2] with rates of 38% to 51% reported in other series.[8,18,19] Moreover, the overall outcomes, other than hospital mortality, such as postoperative LOS, early unplanned reintervention rate, and mid-term mortality rate, in patients weighing <2.5 kg were not greater than those for patients weighing >2.5 kg. Such excellent early and mid-term outcomes reported in our series and by others[4,20] might rely on the expertise acquired by a multidisciplinary team dedicated to neonatal cardiac care in the setting of a high-volume program.

The outcomes of the patients weighing <2.5 kg were independent of the STAT risk category and the uni/biventricular pathway in contrast to those weighing >2.5 kg. Curzon and colleagues[2] demonstrated in the STS database series that a lower weight consistently increased the risk of mortality after risk stratification. Palliation for a univentricular heart, the diagnosis of hypoplastic left heart syndrome, and performance of a Norwood procedure have been reported as risk factors for adverse outcomes after cardiac surgery in low-weight infants.[1-4,8,19,21] The reason for neutralization of the risk categories and univentricular palliation as risk factors in our series does not seem to be explained by a lack of statistical power, because the STAT 5 category group and univentricular pathway group were 2 of the most important groups in our series. The neutralization of these factors in patients weighing <2.5 kg seems to be related to the excellent outcomes in the patients with hypoplastic left heart syndrome (main procedure in the STAT 5 category group and univentricular pathway group) in our series. We speculate that the use of the right ventricle to pulmonary artery conduit conferred a survival advantage to stage I palliation in low-weight patients. In contrast to the Norwood procedure, some specific procedures performed at a weight <2.5 kg still seem to confer a greater risk of early mortality, such as total anomalous pulmonary venous return repair or aortopulmonary shunt for TOF. These findings are also consistent with the STS data,[2] in particular, with respect to mortality after aortopulmonary shunts. The distribution of

prematurity among the STAT categories, surgical strategy groups, and procedures was not equal: patients with a STAT 4 category or palliation toward biventricular repair or aortic arch repair had a lower mean gestational age than those with a STAT 5 category, a univentricular pathway, or a Norwood procedure, which might explain the better outcomes in the STAT 5 category, given that, other than postoperative cardiac arrest, a lower gestational age at birth was the strongest and only risk factor that remained after multivariate analysis.

The ''usual'' or ''delayed'' timing of surgery was not associated with a greater risk of any of the outcomes in this low-weight population, implying at first view that delaying repair of congenital heart defects in low birthweight infants does not seem to confer a benefit. However, it could also mean that the ''delayed'' patients benefitted from the delay, because their outcomes could have been worse had they undergone surgery at a ''usual'' time. These findings are consistent with other published series.[14,21-27] In particular, a study from Toronto[12] showed that for neonates weighing <2.0 kg, imposed delays in intervention neither compromised nor improved survival.

Our multivariate analysis demonstrated that low gestational age at birth was the only independent risk factor for early mortality in the low-weight patients. This major variable could not be studied by Curzon and colleagues,[2] because this variable was not captured by the STS congenital database when that study was performed. However, other studies have suggested a probable negative role played by prematurity in this specific population.[3,9,15,28] Hickey and colleagues[12] showed that gestational age strongly influenced the subsequent risk of death in a predictable way but was not a significant independent risk factor in relation to low birthweight. This risk factor has been confirmed by other studies[29] and should thus be taken into account in the treatment of such patients, such as delaying birth to full maturity whenever possible.

Regarding major extracardiac malformations, reports of their influence on the risk of death in the studied population have been contradictory.[3,4,7,21,30,31] Such an association is perhaps strongest in the subgroup of patients undergoing a Norwood procedure.[8,18] Similarly, the presence of a genetic syndrome was not associated with worse outcomes, in contrast to the report by Azakie and colleagues.[4] This could have been because two thirds of patients with a genetic syndrome had either Down syndrome or DiGeorge syndrome.

The present study was limited by its retrospective nature. We were unable to answer the question of whether a strategy of deferring surgical intervention for maturation is beneficial. The patient population was very heterogeneous; thus, we could not provide much insight into the therapeutic strategies that might be advantageous for a given clinical situation. The short follow-up period of the study did not allow a good analysis of long-term mortality. Finally, the present study did not include patients weighing <2.5 kg admitted for surgical congenital heart disease who did not undergo surgery (n = 4). These 4 patients did not undergo surgery because of a contraindication to cardiopulmonary bypass (severe prematurity-related morbidity in 2) or because they had died with the surgery already scheduled (n = 2).

CONCLUSIONS

Although a weight of <2.5 kg at surgery remains a risk factor for early mortality, a dedicated neonatal cardiac program can yield excellent outcomes for low-weight neonates or infants independently of the STAT risk category, uni/biventricular pathway, and surgical timing. Such good outcomes also extended into the STAT 5 risk category and univentricular pathway. The birthweight, presence of extracardiac malformations, presence of a genetic syndrome, STAT category, surgical strategy, timing of surgery, and surgeon were not associated with an increased risk of hospital mortality. A lower gestational age at birth was a major independent risk factor for early mortality.

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References

1. Pawade A, Waterson K, Laussen P, Karl TR, Mee RB. Cardiopulmonary bypass in neonates weighing less than 2.5 kg: analysis of the risk factors for early and late mortality. *J Card Surg*. 1993;8:1-8.
2. Curzon CL, Milford-Beland S, Li JS, O'Brien SM, Jacobs JP, Jacobs ML, et al. Cardiac surgery in infants with low birth weight is associated with increased mortality: analysis of the Society of Thoracic Surgeons Congenital Heart Database. *J Thorac Cardiovasc Surg*. 2008;135:546-51.
3. Ades AM, Dominguez TE, Nicolson SC, Gaynor JW, Spray TL, Wernovsky G, et al. Morbidity and mortality after surgery for congenital cardiac disease in the infant born with low weight. *Cardiol Young*. 2010;20:8-17.
4. Azakie A, Johnson NC, Anagnostopoulos PV, Egrie GD, Lavrsen MJ, Sapru A. Cardiac surgery in low birth weight infants: current outcomes. *Interact Cardiovasc Thorac Surg*. 2011;12:409-13.
5. Bove T, Francois K, De Groote K, Suys B, De Wolf D, Verhaaren H, et al. Outcome analysis of major cardiac operations in low weight neonates. *Ann Thorac Surg*. 2004;78:181-7.
6. Dimmick S, Walker K, Badawi N, Halliday R, Cooper SG, Nicholson IA, et al. Outcomes following surgery for congenital heart disease in low-birthweight infants. *J Paediatr Child Health*. 2007;43:370-5.
7. Oppido G, Pace Napoleone C, Formigari R, Gabbieri D, Pacini D, Frascaroli G, et al. Outcome of cardiac surgery in low birth weight and premature infants. *Eur J Cardiothorac Surg*. 2004;26:44-53.
8. Pizarro C, Davis DA, Galantowicz ME, Munro H, Gidding SS, Norwood WI. Stage I palliation for hypoplastic left heart syndrome in low birth weight neonates: can we justify it? *Eur J Cardiothorac Surg*. 2002;21:716-20.
9. Rossi AF, Seiden HS, Sadeghi AM, Nguyen KH, Quintana CS, Gross RP, et al. The outcome of cardiac operations in infants weighing two kilograms or less. *J Thorac Cardiovasc Surg*. 1998;116:28-35.
10. Seo DM, Park JJ, Yun TJ, Kim YH, Ko JK, Park IS, et al. The outcome of open heart surgery for congenital heart disease in infants with low body weight less than 2500 g. *Pediatr Cardiol*. 2011;32:578-84.
11. O'Brien SM, Clarke DR, Jacobs JP, Jacobs ML, Lacour-Gayet FG, Pizarro C, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. *J Thorac Cardiovasc Surg*. 2009;138:1139-53.
12. Hickey EJ, Nosikova Y, Zhang H, Caldarone CA, Benson L, Redington A, et al. Very low-birth-weight infants with congenital cardiac lesions: is there merit in delaying intervention to permit growth and maturation? *J Thorac Cardiovasc Surg*. 2012;143:126-36.

13. Beyens T, Biarent D, Bouton JM, Demanet H, Viart P, Dessy H, et al. Cardiac surgery with extracorporeal circulation in 23 infants weighing 2500 g or less: short and intermediate term outcome. *Eur J Cardiothorac Surg*. 1998; 14:165-72.
14. Chang AC, Hanley FL, Lock JE, Castaneda AR, Wessel DL. Management and outcome of low birth weight neonates with congenital heart disease. *J Pediatr*. 1994;124:461-6.
15. Williams GD, Cohen RS. Perioperative management of low birth weight infants for open-heart surgery. *Paediatr Anaesth*. 2011;21:538-53.
16. Alkan-Bozkaya T, Turkoglu H, Akcevin A, Paker T, Ozkan-Cerci H, Dindar A, et al. Cardiac surgery of premature and low birthweight newborns: is a change of fate possible? *Artif Organs*. 2010;34:891-7.
17. Charette K, Hirata Y, Bograd A, Mongero L, Chen J, Quaegebeur J, et al. 180 ml and less: cardiopulmonary bypass techniques to minimize hemodilution for neonates and small infants. *Perfusion*. 2007;22:327-31.
18. Gelehrter S, Fifer CG, Armstrong A, Hirsch J, Gajarski R. Outcomes of hypoplastic left heart syndrome in low-birth-weight patients. *Pediatr Cardiol*. 2011;32:1175-81.
19. Weinstein S, Gaynor JW, Bridges ND, Wernovsky G, Montenegro LM, Godinez RI, et al. Early survival of infants weighing 2.5 kilograms or less undergoing first-stage reconstruction for hypoplastic left heart syndrome. *Circulation*. 1999;100:II167-70.
20. Kopf GS, Mello DM. Surgery for congenital heart disease in low-birth weight neonates: a comprehensive statewide Connecticut program to improve outcomes. *Conn Med*. 2003;67:327-32.
21. Reddy VM, McElhinney DB, Sagrado T, Parry AJ, Teitel DF, Hanley FL. Results of 102 cases of complete repair of congenital heart defects in patients weighing 700 to 2500 grams. *J Thorac Cardiovasc Surg*. 1999;117:324-31.
22. Bacha EA, Almodovar M, Wessel DL, Zurakowski D, Mayer JE Jr, Jonas RA, et al. Surgery for coarctation of the aorta in infants weighing less than 2 kg. *Ann Thorac Surg*. 2001;71:1260-4.
23. Haas F, Goldberg CS, Ohye RG, Mosca RS, Bove EL. Primary repair of aortic arch obstruction with ventricular septal defect in preterm and low birth weight infants. *Eur J Cardiothorac Surg*. 2000;17:643-7.
24. Reddy VM. Low birth weight and very low birth weight neonates with congenital heart disease: timing of surgery, reasons for delaying or not delaying surgery. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2013;16:13-20.
25. Roussin R, Belli E, Bruniaux J, Demontoux S, Touchot A, Planche C, et al. Surgery for transposition of the great arteries in neonates weighing less than 2,000 grams: a consecutive series of 25 patients. *Ann Thorac Surg*. 2007;83: 173-7.
26. Wernovsky G, Rubenstein SD, Spray TL. Cardiac surgery in the low-birth weight neonate: new approaches. *Clin Perinatol*. 2001;28:249-64.
27. Shepard CW, Kochilas LK, Rosengart RM, Brearley AM, Bryant R III, Moller JH, et al. Repair of major congenital cardiac defects in low-birth-weight infants: is delay warranted? *J Thorac Cardiovasc Surg*. 2010;140:1104-9.
28. Cheng HH, Almodovar MC, Laussen PC, Wypij D, Polito A, Brown DW, et al. Outcomes and risk factors for mortality in premature neonates with critical congenital heart disease. *Pediatr Cardiol*. 2011;32:1139-46.
29. Costello JM, Polito A, Brown DW, McElrath TF, Graham DA, Thiagarajan RR, et al. Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. *Pediatrics*. 2010;126:277-84.
30. Dees E, Lin H, Cotton RB, Graham TP, Dodd DA. Outcome of preterm infants with congenital heart disease. *J Pediatr*. 2000;137:653-9.
31. Numa A, Butt W, Mee RB. Outcome of infants with birthweight 2000 g or less who undergo major cardiac surgery. *J Paediatr Child Health*. 1992;28:318-20.

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EDITORIAL COMMENTARY

Timing is even more important than we thought! The effect of gestational age versus body weight on outcomes of neonatal heart surgery

Osman O. Al-Radi, MD, MSc, FRCSC

See related article on pages 2499-506.

The outcomes of heart surgery for neonates have improved dramatically over the last few decades. Significant incremental improvements in our understanding of the pathophysiology, as well as surgical techniques and perioperative care, have contributed to this positive change. However, both low body weight and prematurity are still recognized predictors of adverse outcomes in these patients.[1,2] It is somewhat challenging to differentiate which of the 2 factors has more predictive power because the 2 factors are correlated and there is significant variability in how these 2 seemingly simple measures are recorded and reported in databases and in the literature. The size of the child undergoing surgery is reported in variable forms including body weight, body surface area, or less frequently birth weight. There is even more variability in the reporting of prematurity. The spectrum includes reporting gestational age in weeks (mostly not including added days), a binary designation as premature at a certain cutoff point, or no reporting on prematurity whatsoever.

This differentiation between weight and prematurity is probably important. Theoretically, body weight is a technical challenge that can be overcome by improvements

From the Department of Surgery, King Abdulaziz University, Jeddah, Saudi Arabia.
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Address for reprints: Osman O. Al-Radi, MD, MSc, FRCSC, Department of Surgery, PO Box 80215, Building 10, room 1027, Jeddah, Makkah Province 21589, Saudi Arabia (E-mail: oradi@kau.edu.sa).
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TABLE E1. Frequency of main procedures

Procedure	Group 1 (<2.5 kg; n = 146)	Group 2 (2.5-4.5 kg; n = 622)	*P* value
Single ventricle			
Norwood	25 (17)	141 (22.7)	.14
Conduit or shunt	9 (6.2)	36 (5.8)	1
Isolated atrial septectomy	1 (0.7)	1 (0.2)	1
PA band	3 (2)	12 (1.9)	1
Right-side heart lesions			
TOF, PA, VSD			
Primary repair	12 (8.2)	30 (4.8)	.11
Shunt palliation or unifocalization	12 (8.2)	20 (3.2)	.01*
PA-IVS			
RVOT repair	2 (1.4)	8 (1.3)	1
Shunt palliation	2 (1.4)	10 (1.6)	1
Pulmonary stenosis repair	2 (1.4)	3 (0.5)	.24
Aortic arch lesions			
Coarctation-hypoplastic arch: aortic arch repair	8 (5.5)	57 (9.2)	.19
Coarctation-VSD: aortic arch + VSD repair	8 (5.5)	32 (5.1)	1
Interrupted aortic arch repair	6 (4.1)	23 (3.7)	.81
Simple/complex TGA			
TGA-IVS: ASO	13 (8.9)	85 (13.7)	.13
TGA-VSD: ASO + VSD closure	8 (5.5)	33 (5.3)	1
TGA-VSD-PS			
Complete repair	1 (0.7)	7 (1.1)	1
Palliation	0	6 (1)	.62
Other			
TAPVR repair	9 (6.2)	47 (7.6)	.6
VSD			
Primary repair	8 (5.5)	19 (3)	.2
PA band	1 (0.7)	0	.2
Truncus arteriosus			
Repair	7 (4.8)	14 (2.2)	.1
PA band	1 (0.7)	0	.19
AVSD			
Primary repair	2 (1.4)	3 (0.5)	.24
PA band	0	1 (0.2)	1

Data presented as n (%). *PA*, Pulmonary artery; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect; *IVS*, intact ventricular septum; *RVOT*, right ventricular outflow tract; *TGA*, transposition of the great arteries; *ASO*, arterial switch operation; *PS*, pulmonary stenosis; *TAPVR*, total anomalous pulmonary venous return; *AVSD*, atrioventricular septal defect. *Statistically significant.