Older children at the time of the Norwood operation have ongoing mortality vulnerability that continues after cavopulmonary connection

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Objectives: Delayed first-stage palliation of children with hypoplastic left heart syndrome and related pathologies can be associated with poor outcomes because of development of progressive pulmonary vascular disease and volume load effects on the systemic ventricle and atrioventricular valve. We examine the current era's survival in this subgroup.

Methods: Fifty-five infants older than 2 weeks underwent the Norwood operation (2003–2007). Separate competing risk analyses were performed to model outcomes (death and transition to the next stage) after the Norwood operation and after bidirectional cavopulmonary connection.

Results: Median age was 32 days (range, 15–118 days). Forty-seven percent had hypoplastic left heart syndrome, and 53% had other complex univentricular variants. Mean ascending aortic size was 4.4 ± 1.9 mm, 10% had impaired ventricular function, 11% had moderate atrioventricular valve regurgitation, and 32% had restrictive pulmonary venous return. Pulmonary blood flow was established through an aortopulmonary shunt ($n = 30$) or Sano shunt ($n = 25$). After the Norwood operation, patients required longer ventilation and more oxygen and nitric oxide and had higher inotropic scores compared with those undergoing the traditional management protocol. Competing risks analysis showed that 2 years after the Norwood operation, 39% had died, and 57% underwent bidirectional cavopulmonary connection. Four years after bidirectional cavopulmonary connection, 15% had died, and 85% underwent the Fontan operation. Overall 3-year survival after the Norwood operation was 53%. Factors associated with mortality were age, lower weight at the time of the Norwood operation, impaired ventricular function, longer circulatory arrest, and lower pre-bidirectional cavopulmonary connection saturation.

Conclusions: Children older than 2 weeks undergoing the Norwood operation frequently require postoperative pulmonary vasodilatation and high inotropic support. A significant hazard of death persists through all steps of multistage palliation. Increased pulmonary vascular resistance and volume load effects, such as systemic ventricular impairment and atrioventricular valve regurgitation, are commonly evident in patients in whom treatment fails or who do not qualify to proceed to the next stage of palliation. Those patients should be closely monitored for timely referral for heart transplantation when indicated. (J Thorac Cardiovasc Surg 2011;142:142–7)

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Multistage palliation is currently the standard treatment for hypoplastic left heart syndrome (HLHS) and other related

complex, single-ventricle malformations in the majority of cardiac centers.^{1–6} Results of first-stage palliation have significantly improved in the last decade because of refinements in preoperative care, surgical and perfusion techniques, postoperative care, and monitoring.^{7–15}

Several previous reports have demonstrated that first-stage palliation performed in infants older than 2 to 4 weeks of age is associated with a significant increase in mortality.^{2–4,6,16} This was ascribed to the development of pulmonary vascular disease, which complicated the postoperative course and predisposed the infants to potentially fatal pulmonary hypertensive crises in addition to the effects of prolonged volume load on the single ventricle with subsequent dysfunction and on the atrioventricular valve (AVV) with subsequent regurgitation, with a significant negative effect on early and late outcomes.^{17,18}

Despite multiple existing current large series demonstrating improved results of first-stage palliation, the number of

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Abbreviations and Acronyms

AVV	= atrioventricular valve
BCPC	= bidirectional cavopulmonary connection
ECMO	= extracorporeal membrane oxygenation
F _{IO₂}	= fraction of inspired oxygen
HLHS	= hypoplastic left heart syndrome
mBTS	= modified Blalock–Taussig shunt
PE	= parameter estimate
PVR	= pulmonary vascular resistance
RV–PA	= right ventricle–pulmonary artery
SE	= standard error

infants older than 2 weeks at the time of first-stage palliation in those series is small because the majority of those patients undergo surgical intervention within the first week of age.^{7–15} In the present report we aim to describe the outcomes of infants older than 2 weeks of age at the time of first-stage palliation in the current era and examine factors associated with increased hazards of mortality.

MATERIALS AND METHODS

Inclusion Criteria

From 2003 to 2007, 55 consecutive infants with variable single-ventricle pathologies underwent Norwood-type first-stage palliation at an age of greater than 14 days at the King Faisal Specialist Hospital and Research Center in Riyadh, Saudi Arabia. Clinical, operative, and outcome data were abstracted from patients' medical records. Approval of this study was obtained from the research ethics board at our institution, and requirement for individual consent was waived for this observational study.

Operative Details

The surgical procedure consisted of standard first-stage Norwood palliation with division of the main pulmonary artery and side-to-side anastomosis with the ascending aorta, aortic arch augmentation and reconstruction, and atrial septectomy. Pulmonary blood flow was established with either a modified Blalock–Taussig shunt (mBTS) or a right ventricle–pulmonary artery (RV–PA) conduit based on the individual surgeon's preference. During arch reconstruction, deep hypothermic circulatory arrest and selective antegrade cerebral perfusion, isolated or in combination, were used at the surgeon's discretion.

Follow-up

Time-related outcomes were determined from recent office visits at King Faisal Specialist Hospital and Research Center and from direct correspondence with patients' families. Follow-up was complete. Mean follow-up was 2.2 ± 2.1 years for the entire cohort and 2.8 ± 2.0 years for patients who survived to hospital discharge after the first stage.

Statistical Analysis

Data are presented as means with standard deviations, medians with minimums and maximums, and frequencies, as appropriate. Time-dependent mutually exclusive outcomes (death and survival to the next stage of palliation) after first-stage palliation and after bidirectional cavopulmonary connection (BCPC) were parametrically modeled. Parametric probability estimates for time-dependent outcomes use models based on multiple overlapping phases of risk (available for use with the SAS system

at <http://www.clevelandclinic.org/heartcenter/hazard>). The HAZARD procedure uses maximum likelihood estimates to resolve risk distribution of time to event in up to 3 phases of risk (early, constant, and late). Competing risk analysis was performed to model the probability over time of each of 2 mutually exclusive end points after first-stage palliation and after BCPC: death and survival to the next stage of palliation and the remaining patients beginning alive and not qualifying for the next stage of palliation. Variables potentially influencing the likelihood of outcomes in the competing risk models were sought from demographic, anatomic, and surgical variables through a stepwise regression algorithm ($P < .05$ to enter) for each phase of risk. Effects of covariates on the probability of outcomes in competing risk models are given as parameter estimates (PEs) and standard errors (SEs). The clinical relevance of covariates of interest on likelihood of selected outcomes was established by solving the regression equations for multiple "typical" test patients. All statistical analyses were performed with SAS statistical software version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Cohort

During the study period, 55 infants older than 14 days underwent Norwood-type first-stage palliation. There were 37 (65%) male and 18 (35%) female patients. The age range was 15 to 118 days and included 12 patients 2 to 3 weeks old, 12 patients 3 to 4 weeks old, and 31 patients more than 4 weeks old. Complete patients' characteristics are detailed in Table 1.

First-Stage Palliation

At the time of first-stage palliation, pulmonary blood flow was restored by means of mBTS in 29 (54%) patients and by means of an RV–PA conduit in 24 (44%) patients, with 1 (2%) patient requiring both. One patient in whom the shunt type is not well documented died in the operating room. Mean mBTS diameter was 3.9 ± 0.3 mm, and mean RV–PA conduit size was 5.7 ± 0.5 mm. Mean cardiopulmonary bypass time was 139 ± 43 minutes, mean aortic cross-clamp time was 68 ± 20 minutes, and mean deep hypothermic circulatory arrest time was 42 ± 22 minutes.

Five patients required postoperative extracorporeal membrane oxygenation (ECMO), and none of them survived. Three patients required shunt revision, and 2 of them died. Other reoperations included diaphragmatic plication in 5 patients and evacuation of a seroma compressing on the shunt and pulmonary arteries in 1 patient.

Inotrope use was quantified by a revised score adapted from Wernovsky and colleagues.¹⁹ The score was calculated by obtaining the average amount of inotropic support the patients received at the first 3 postoperative days (excluding patients receiving ECMO support) and then entering the data into the following equation:

$$\text{Inotrope score} = \text{Dopamine} + \text{Dobutamine} + ([\text{Epinephrine} + \text{Norepinephrine}] \times 100) + (\text{Milrinone} \times 20).$$

Units of inotrope dosage used in this equation were in micrograms per kilogram per minute. The average inotropic

TABLE 1. Complete characteristics for the entire patient cohort (n = 55)

Age at first-stage palliation (d), median (range)	32 (15–118)
Male sex, n (%)	37 (65)
Mean weight (kg)	3.1 ± 0.6
Diagnosis	
HLHS, n (%)	26 (47%)
Non-HLHS, n (%)	29 (53%)
Double-inlet left ventricle	11
Double-outlet right ventricle	6
Severe Shone complex	3
Unbalanced atrioventricular septal defect	2
Tricuspid atresia	2
Other	5
Dominant ventricular morphology, n (%)	
Left	17 (31%)
Right	38 (69%)
Dominant ventricular function	
Normal	90%
Mildly impaired	4%
Moderately impaired	6%
Dominant atrioventricular valve function	
Competent or trivial regurgitation	63%
Mild regurgitation	26%
Moderate regurgitation	11%
Aortic atresia	28%
Mitral atresia	31%
Restrictive pulmonary venous return	32%
Ascending aortic diameter (mm)	4.4 ± 1.9
Situs inversus/dextrocardia	1
Interrupted aortic arch	2
Genetic syndrome	0
Extracardiac malformations	0

HLHS, Hypoplastic left heart syndrome.

score in the first 3 days was 38 ± 26 per day and was lower for first-stage survivors (32 ± 14 per day) versus nonsurvivors (58 ± 44 per day, $P < .0001$). The average oxygen saturation in the first 3 days was $70\% \pm 6\%$, and the average fraction of inspired oxygen (F_{IO_2}) was $50\% \pm 16\%$. Nitric oxide use was required in 12 patients. Median ventilation duration in first-stage survivors was 18 days (range, 2–108 days).

The difference in postoperative parameters between first-stage hospital survivors versus nonsurvivors is shown in Table 2.

Competing Risk Analysis After First-Stage Palliation

After the 55 initial Norwood-type first-stage palliative procedures, 31 (56%) patients underwent BCPC, and 22 (40%) patients died before BCPC. In addition, 1 (2%) patient in whom the superior vena cava was obstructed proceeded immediately to the Fontan operation and, 1 (2%) remaining patient remains alive but did not qualify for BCPC because of severe neurologic insult after a central nervous system infection that was unrelated to the cardiac procedure.

The competing risks analysis after first-stage palliation showed that at 1 year after first-stage palliation, approximately 37% of patients had died, and 54% had undergone BCPC. By 2 years after first-stage palliation, 39% have died, and 58% have proceeded to the next stage of palliation (Figure 1).

Factors associated with higher mortality after first-stage palliation were sought, and results are shown in Table 3. Significant factors for mortality included lower weight (PE, +0.84 [SE, 0.41]; $P = .04$), longer deep hypothermic circulatory arrest (PE, +0.20 [SE, 0.09]/10 min; $P = .03$), impaired dominant ventricular function (PE, +1.20 [SE, 0.57]; $P = .04$), and age category less than 3 weeks (PE, +1.05 [SE, 0.46], $P = .03$).

Competing Risks Analysis After Second-Stage Palliation

Thirty-one patients underwent BCPC. Hemodynamic and echocardiographic parameters before BCPC are listed in Table E1. BCPC was right sided (n = 28), left sided (n = 1), and bilateral (n = 2). Eight patients had preparation for a subsequent interventional Fontan operation at the time of BCPC. Additional cardiac procedures were performed in 15 patients and included pulmonary artery augmentation (n = 12), arch augmentation (n = 1), AVV repair (n = 2), AVV closure (n = 1), and permanent pacemaker insertion (n = 1). One patient required postoperative takedown of the BCPC and placement of an mBTS because of increased pulmonary vascular resistance (PVR).

After the 31 BCPC procedures, 26 (84%) patients underwent the Fontan procedure, and 5 (16%) patients died before the Fontan procedure. The competing risks analysis after second-stage palliation showed that at 2 years after second-stage palliation, approximately 15% of patients had died, and 43% had undergone the Fontan procedure, with the remaining 43% alive and awaiting the Fontan

TABLE 2. Postoperative care parameters after first-stage palliation in infants older than 2 weeks at the time of the operation

	Overall	Survivors	Nonsurvivors	P value
Average 3-d inotropic score*	38 ± 26/d	32 ± 14/d	58 ± 44/d	<.0001
Average 3-d oxygen saturation	70% ± 6%	71% ± 6%	68% ± 9%	.02
Average 3-d F_{IO_2} use	50% ± 16%	48% ± 14%	58% ± 20%	.10
Average 3-d oxygen saturation/ F_{IO_2} ratio	1.6 ± 0.6	1.6 ± 0.6	1.4 ± 0.7	.50
Nitric oxide use	12 patients	7 patients	5 patients	

All units are in micrograms per kilogram per minute. F_{IO_2} , Fraction of inspired oxygen. *Inotrope score: Dopamine + Dobutamine + [(Epinephrine + Norepinephrine) × 100] + (Milrinone × 20).

FIGURE 1. Competing risks depiction of events (death and transition to bidirectional cavopulmonary connection, with the remaining few patients alive and awaiting bidirectional cavopulmonary connection or transitioning directly to the Fontan operation) after Norwood-type first-stage palliation of HLHS and related pathologies in infants greater than 2 weeks of age.

procedure. By 4 years after second-stage palliation, 15% have died, and the remaining 85% have proceeded to the Fontan procedure (Figure 2).

Factors associated with higher mortality after BCPC were sought, and results are shown in Table 3. Significant factors for mortality included smaller ascending aortic size (PE, +0.82 [SE, 0.42]/mm; $P = .05$), higher pre–Glenn procedure transpulmonary gradient (PE, +0.20 [SE, 0.11]/mm Hg; $P = .06$), and age category less than 3 weeks at

TABLE 3. Risk factors for death in patients older than 2 weeks at first-stage palliation

	Parameter estimate (standard error)	P value
1. Factors associated with death after the Norwood operation (before BCPC)		
Longer DHCA time (per 10 min)	0.20 (0.09)	.03
Lower weight at time of operation (per kg)	0.84 (0.41)	.04
Impaired dominant ventricular function	1.20 (0.57)	.04
Age group <3 wk	1.05 (0.46)	.03
2. Factors associated with death after BCPC (before the Fontan procedure)		
Higher transpulmonary gradient	0.20 (0.10)	.06
Smaller ascending aortic size	0.82 (0.42)	.05
Age group <3 wk at time of Norwood operation	1.94 (0.92)	.04
3. Factors associated with overall mortality		
Age group <3 wk at time of Norwood operation	0.48 (0.24)	.05
Impaired dominant ventricular function	0.99 (0.53)	.06
Lower weight category (<2.5 vs >2.5 kg)	0.57 (0.32)	.07
Longer DHCA time (min)	0.03 (0.01)	.01
Lower oxygen saturation before BCPC (per %)	0.06 (0.04)	.09

DHCA, Deep hypothermic circulatory arrest; BCPC, bidirectional cavopulmonary connection.

FIGURE 2. Competing risks depiction of events (death and transition to the Fontan operation) after bidirectional cavopulmonary connection (BCPC) in infants who underwent Norwood-type first-stage palliation at greater than 2 weeks of age.

the time of the Norwood operation (PE, +1.94 [SE, 0.92]; $P = .04$).

Of note, 3 patients died after the Fontan procedure, 2 in the perioperative period and 1 after reoperation for pulmonary venous obstruction. Hemodynamic and echocardiographic parameters before the Fontan procedure are listed in Table E1.

Overall Survival

Overall 3-year survival after first-stage palliation was 53%. The hazard function for death was characterized by a pronounced early hazard phase in the immediate postoperative period but a persistent constant hazard phase that continued up to 1.5 years after first-stage palliation (Figure 3).

Factors associated with overall mortality are shown in Table 3. The relationship between overall survival and patient weight at the time of the operation is shown in Figure E1. Of note, there were trends for decreased survival in patients with dominant right ventricular morphology (Figure E2) and with the use of an RV–PA conduit (Figure E3), although those trends did not reach statistical significance. The events after first-stage palliation in the entire cohort of patients is shown in Figure E4.

DISCUSSION

Despite multiple reports from different institutions demonstrating significant improvement in hospital survival after first-stage palliation of HLHS and other complex single-ventricle pathologies, little information is available regarding contemporary outcomes in infants older than 2 weeks at the time of the operation.⁷⁻¹⁵ Older age was identified as a significant risk factor for hospital and interstage mortality

FIGURE 3. Time-dependent survival (A) and hazard risk of death (B) over time after Norwood-type first-stage palliation. The hazard function for death is characterized by the presence of an early hazard phase during the initial few months after surgical intervention. After that period, there is a constant attrition that continues up to 2 years after the initial operation. The *solid lines* in the parametric model represent parametric point estimates, and the *dashed lines* enclose the 95% confidence interval. *Circles* represent nonparametric estimates.

in many prior reports.^{2-4,6,16} Nonetheless, most available current large series contain few patients older than 2 weeks at the time of the Norwood operation, and therefore it is not clear whether this subgroup of patients benefited from this recent trend of superior results.⁷⁻¹⁵

At our institution, we continue to assess many patients with various complex single-ventricle anomalies at older ages because of the tertiary nature of our practice as the sole provider for Norwood-type palliation in the region. Our unique experience prompted us to review contemporary outcomes in a relatively large consecutive cohort of older infants at the time of first-stage palliation. Surgical delays in our current series were not related in general to poor pre-operative status, sepsis, or multiorgan failure but rather to late presentation or referral.

One of our principal findings was the distinctive postoperative course in this subgroup of patients. The mainstay of postoperative treatment after the Norwood operation is achieving a balance between the pulmonary and systemic circulations. Systemic afterload reduction and ventilator management to avoid pulmonary overcirculation are commonly used in the postoperative care of neonates after the Norwood operation.^{7,14,15} In our older patients, however, a different treatment philosophy is often required. Many of our patients exhibit signs of poor pulmonary circulation and require high oxygen concentrations and pulmonary vasodilators, such as nitric oxide, to promote blood flow to the lungs. In addition, there is often very little room for systemic vasodilatation, and those infants often require inotropic support and vasopressors, as demonstrated by the high inotropic score in the initial 3 postoperative days. This distinct postoperative requirement can be explained by the effects of delayed surgical intervention, such as the development of progressive pulmonary vascular disease, chronic volume load causing development of postoperative ventricular dysfunction, or AVV regurgitation. Moreover, older infants in our series required high oxygen concentration, had low oxygen saturation, and required prolonged ventilation and subsequent prolonged intensive care unit and hospital stays. ECMO support was largely ineffective in our patient population, especially because the heart transplantation option was not offered to this age group at our institution.

Additionally, we noted a high interstage mortality in our patient cohort, with only 60% of all patients proceeding to the next stage of palliation. This high interstage mortality in older infants has been noted by other investigators. Hehir and colleagues¹⁶ showed that the Norwood operation at greater than 7 days of age is a significant risk factor for interstage mortality. In addition to residual lesions and shunt-related problems,^{13,20} high PVR and a reactive pulmonary vascular bed expose those infants to the risk of pulmonary hypertension crises that can be often fatal and might be implicated in this high occurrence of interstage mortality. We have noted many incidents of pulmonary hypertension in our patient cohort while in the hospital with subsequent respiratory and hemodynamic compromise, cardiac arrest, and occasional mortality. This tendency likely continues after discharge to contribute to this disturbingly high rate of sudden death at home.

Although the risk of mortality is usually greatly eliminated when a balanced circulation is achieved by means of BCPC with eradication of shunt problems, coronary steal risk, volume load effects, and management of any residual lesions.^{3,6,13} In our series we observed that those older patients do not enjoy this stabilization of mortality risk with time, and the hazard of death continues after BCPC almost up to 2 years after the Norwood procedure. Pulmonary vascular disease, ventricular dysfunction, and

AVV regurgitation were evident in most patients who did not progress to the next stage of palliation or died after subsequent palliative procedures in our series. This finding highlights the importance of continued close follow-up of those patients for timely referral for heart transplantation when indicated.

Several demographic, anatomic, operative, and hemodynamic variables were analyzed to determine factors that significantly affect survival. Some trends that did not reach statistical significance merit some discussion. We have noted that patients who received mBTSs as a source of pulmonary blood flow at the time of first-stage palliation had a trend for improved survival compared with those who received RV-PA conduits. Although RV-PA conduits have been shown to facilitate postoperative care and even to decrease early mortality in some series,^{8,11,12} this was not the case in older patients in our series. The benefit of the RV-PA conduit is diluted in this subgroup of patients in whom pulmonary overcirculation and subsequent coronary steal are not major problems. In addition, lower saturations achieved by the RV-PA conduit, especially in the setting of increased PVR, and the effects of ventriculotomy, especially in those patients with ventricular dysfunction caused by chronic volume load, might all contribute to the surprisingly worse survival seen in older patients who received RV-PA conduit.

We have also noted that patients with dominant left ventricular morphology had a trend toward improved survival. This finding might be explained by the fact that morphologic left ventricles are more equipped to tolerate higher afterload and volume load and therefore might be more resilient to the sequelae of delayed first-stage palliation.

Of interest, the outcomes in the oldest patients in our series, those older than 4 weeks, were not worse than those 2 to 4 weeks old. This might be explained by a more selective approach to the older patients at our institution but definitely highlights that the development of pulmonary vascular disease is unpredictable and that the relationship between PVR and age in days is not linear, at least within the age margins of our patient cohort.

In conclusion, infants older than 2 weeks at the time of Norwood-type first-stage palliation comprise a unique subgroup of patients. Postoperative care is different from traditional management, with a higher likelihood of requirement of inotropes, vasopressors, and pulmonary vasodilators. Despite improved outlook of patients undergoing Norwood-type operations in the recent era, older infants at the time of first-stage palliation continue to be exposed to the hazard of death that continues beyond the perioperative and interstage periods and throughout all steps of multistage palliation. This vulnerability is mostly the product of delayed operation because of the development of pulmonary vascular disease and ventricular dysfunction. Careful preoperative assessment of those infants is necessary for selection

of the most appropriate procedure, and vigilant follow-up is necessary for timely referral for heart transplantation, as indicated in patients not proceeding to the next stage of palliation.

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FIGURE E1. Parametric model for survival after first-stage palliation stratified by weight group at the time of the initial operation. Lower weight was associated with higher mortality.

FIGURE E3. Parametric model for survival after first-stage palliation stratified by the type of shunt at the time of first-stage palliation. There was a trend for improved survival in patients who had a modified Blalock–Taussig shunt compared with that seen in patients who had a right ventricle–pulmonary artery conduit (Sano shunt).

FIGURE E2. Parametric model for survival after first-stage palliation stratified by dominant ventricular morphology. There was a trend for improved survival in patient with dominant left ventricular morphology compared with that seen in patients with dominant right ventricular morphology.

FIGURE E4. Flow chart depicting events after first-stage Norwood-type palliation in 55 infants older than 2 weeks of age at the time of the operation. BCPC, Bidirectional cavopulmonary connection.

TABLE E1. Echocardiographic and hemodynamic parameters before BCPC and before the Fontan procedure

	Pre-BCPC (n = 33)	Pre-Fontan (n = 27)
Mean PA pressure (mm Hg)	17 ± 5	14 ± 3
Mean ventricular EDP (mm Hg)	10 ± 3	10 ± 3
Mean transpulmonary gradient (mm Hg)	7 ± 5	4 ± 3
PVR index (Woods units)	2.3 ± 1.2	1.7 ± 0.8
Oxygen saturation (%)	70 ± 8	83 ± 5
AVV regurgitation	Mild = 17 (52%) Moderate = 3 (9%)	Mild = 3 (11%) Moderate = 2 (7%)
Dominant ventricular function	Mildly impaired = 3 (9%) Moderately impaired = 3 (9%)	Mildly impaired = 2 (7%) Moderately impaired = 0 (0%)

BCPC, Bidirectional cavopulmonary connection; EDP, end-diastolic pressure; PVR, pulmonary vascular resistance; AVV, atrioventricular valve.