PREOPERATIVE RISK-OF-DEATH PREDICTION MODEL IN HEART SURGERY WITH DEEP HYPOTHERMIC CIRCULATORY ARREST IN THE NEONATE

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Objective: Our goal was to generate a preoperative risk-of-death prediction model in selected neonates with congenital heart disease undergoing surgery with deep hypothermic circulatory arrest. **Methods:** We completed a single-center, prospective, randomized, double-blind, placebo-controlled neuroprotection trial in selected neonates with congenital heart disease requiring operations for which deep hypothermic circulatory arrest was used. An extensive database was generated that included preoperative, intraoperative, and postoperative variables. Variables (delivery, maternal, and infant related) were evaluated to produce a *preoperative* risk-of-death prediction model by means of logistic regression. An *operative* risk-of-death prediction model including duration of deep hypothermic circulatory arrest was also generated. **Results:** Between July 1992 and September 1997, 350 (74%) of 473 eligible infants were enrolled with 318 undergoing deep hypothermic circulatory arrest. The mortality was 52 of 318 (16.4%), unaffected by investigational drug. The resulting preoperative risk model contained 4 variables: (1) cardiac anatomy (two-ventricle vs single ventricle surgery, with/without arch obstruction), (2) 1-minute Apgar score (≤ 5 vs > 5), (3) presence of genetic syndrome, and (4) age at hospital admission for surgery (≤ 5 or > 5 days). Mortality for two-ventricle repair was 3.2% (4/130). Mortality for single ventricle palliation was 25.5% (48/188) and was significantly influenced by Apgar score, genetic diagnosis, and admission age. The preoperative model had a prediction accuracy of 80%. The operative risk model included duration of deep hypothermic circulatory arrest, which significantly ($P = .03$) increased risk of death, with a prediction accuracy of 82%. **Conclusions:** In this selected population, postoperative mortality risk is significantly affected by preoperative conditions. Identification of infants with varying mortality risks may affect family counseling, therapeutic intervention, and risk stratification for future study designs. (J Thorac Cardiovasc Surg 2000; 119:347-57)

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More than one third of the 30,000 infants with congenital heart disease (CHD) born in the United States each year require surgical intervention in early infancy.¹⁻³ The factors that influence immediate postoperative mortality are not completely understood. Many previous investigations have focused primarily on specific anatomic entities, the contributions of different surgical techniques, and the conduct of cardiac anesthesia. For many forms of CHD, heart surgery in the neonate necessitates both cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA), which may independently confer time-dependent risks.^{4,5} The durations of CPB and DHCA themselves are dependent on the complexity of the defective anatomy, the medical status of the infants, and the skill of the surgeon. Consequently, the risk contributions attributed to CPB and DHCA are difficult to quantify.

The immediate modes of death after heart surgery in the neonate are generally known and include cardiac arrhythmias, shock, hemorrhage, and sepsis. However, a comprehensive method of quantifying preoperative mortality risks is not available. This study was conducted to determine whether preoperative characteristics could be identified that significantly affect mortality and to examine their relative contribution to death risk. The final purpose was to formulate a simple, broadly applicable risk-of-death prediction model across the spectrum of CHD.

Methods

Study population. Newborn infants admitted to the Cardiac Center of The Children's Hospital of Philadelphia from July 1992 to September 1997 for evaluation of CHD were screened for enrollment into a pharmacologic neuroprotection trial, the context in which the preoperative risk-of-death models were developed. The study was conducted as a single-center, stratified, randomized, blinded, placebo-controlled trial with study drug administered before, during, and after heart surgery with DHCA in the neonate.

Infants were enrolled in the trial and consequently were the target population of the risk model building if they satisfied the following criteria: congenital heart defect necessitating an operation in which DHCA was the chosen perfusion strategy; conceptional age* less than 45 weeks; absence of coincident lethal genetic disorders or severe multiple congenital abnormalities; and informed consent provided. Infants were excluded for the following reasons: neurologic unassessability (from neuromuscular blockade), seizures or coma, elevated liver function tests, neutropenia, or if enrollment would have occurred less than 16 hours before the operation. The

study protocol was approved by the Committee for the Protection of Human Subjects.

William I. Norwood and Marshal L. Jacobs performed the operations during approximately the first half of the trial and Thomas L. Spray and J. William Gaynor performed the remainder. The surgical techniques were not standardized, although the Norwood procedure was performed for patients with hypoplastic left heart syndrome and single ventricle. Cardiac anesthesia was uniformly maintained during the trial, including alpha-stat acid-base management.

Data collection. A comprehensive database was generated, including clinical observations, laboratory values, imaging examinations, and neurodevelopmental test results. The database was temporally organized into three periods: (1) preoperative, (2) intraoperative, and (3) postoperative.

Preoperative observations. The general categories of preoperative information examined are provided in Table I. Categories were chosen because of their plausible relationship to survival and neurologic outcome and the reliable quality of the data. Preoperative observations included demographic data, maternal/fetal characteristics of gestation, and labor and delivery. Demographic data included mother's race, age, parity, socioeconomic status (Hollingshead index⁶), and the presence of maternal health conditions. Characteristics of the infants included gestational age, birth weight, sex, Apgar scores, age at admission to The Children's Hospital of Philadelphia, microcephaly (head circumference $\leq$ 2nd percentile for age), and the presence of a genetic or chromosomal syndrome. Diagnoses were based on a clear constellation of clinical findings to name a specific genetic syndrome (eg, Goldenhar) or abnormal chromosomal analysis (eg, 22q11 deletion). Other infants had definite dysmorphic features (eg, cleft palate) but not a specific, named genetic syndrome. The medical status of the heart, lungs, kidneys, liver, gastrointestinal tract, and bone marrow was also recorded.

The congenital heart defects of the infants were classified into 1 of 4 categories on the basis of preoperative echocardiograms: class I, two-ventricle heart without arch obstruction; class II, two-ventricle heart with arch obstruction; class III, single ventricle heart without arch obstruction, and class IV, single ventricle heart with arch obstruction.

Intraoperative and postoperative observations. Characteristics of the intraoperative period included the duration of surface cooling, lowest recorded nasopharyngeal temperature, duration of CPB cooling, DHCA time, duration of rewarming on CPB, need for additional CPB, and the use of modified ultrafiltration. Postoperative clinical end points for the neuroprotection trial were recorded during the intensive care unit stay, not to exceed 6 weeks after the operation. Observations included the occurrence of death, seizures, coma, and cardiac events.

Statistical considerations. The study population is characterized by the number of infants available for each variable, means and standard deviations for continuous data, and frequencies and proportions for categorical data. Exact 95% confidence intervals are presented for some proportions.

Model building was iterative, integrating clinical knowl-

*Age since conception is determined by adding legal age (time from birth) to estimated gestational age (eg, the conceptional age of a 3-week-old, 37-week estimated gestational age infant is 40 weeks).

Table I. Preoperative variables examined

Demographics (n = 3)	Newborn characteristics (n = 13)	Maternal characteristics (n = 11)	Early neonatal course (n = 23)
Race	Birth weight	Chronic circulatory	Toxic-metabolic-infectious
Sex	Gestational age	Anemia	Hypoglycemia and hyperglycemia
Hollingshead score	Size for dates	Hypertension	Hyponatremia and hypernatremia
	Delivery mode: cesarean section vs vaginal	Pre-eclampsia	Hypomagnesemia and hypermagnesemia
	Apgar score at 1 min	Diabetes	Infection (eg, sepsis, meningitis, pneumonia)
	Apgar score at 5 min	Placental insufficiency	Necrotizing enterocolitis
	Delivery room resuscitation	Infection	Liver dysfunction
	Meconium passage/staining	Urinary tract	Renal dysfunction
	Microcephaly	Sexually transmitted diseases	Cardiorespiratory-circulatory
	Genetic syndrome or chromosomal abnormality	Chorioamnionitis	Age at hospital admission
	Family history of seizures/ cerebral palsy	Drug exposure	Metabolic acidosis
	Oligohydramnios	Alcohol	Cardiac or respiratory arrest
	Polyhydramnios	Tobacco	Congestive heart failure
		Illicit drugs	Anatomic class of CHD (class I, II, III, or IV)
			Blood pressure instability/shock
			Respiratory insufficiency
			Pneumothorax
			Assigned cardiothoracic surgeon (S1, S2, S3, S4)
			Neurologic
			Hydrocephalus
			Brain infarction
			Brain hemorrhage
			Hypotonia
			Lethargy
			Hypothermia

edge and results of statistical analyses, with the intent of creating a broadly applicable parsimonious model. Because there were 52 deaths in the database it was determined a priori that a maximum of 5 prediction variables (10:1 ratio) would be allowed in the final preoperative risk prediction model. The logistic regression model⁷ was used for selecting variables and characterizing their strength of associations with death, using the odds ratio and 95% confidence intervals. Logistic regression models the proportion of deaths and how these proportions are influenced by predictor variables. Mean values were substituted for candidate predictor variables with 5% or fewer missing values.

Categorical variables were formatted with the use of customary dummy variables structure. Dichotomous variables were coded as zero and one, with zero being the reference category. For exploration of initial models, ordinal and continuous (interval scaled) scaled data from the entire data set (Table I) were evaluated as collected or transformed by means of the natural logarithm for continuous data. Sums of binary variables representing maternal and infant infections, ischemic conditions, and cardiac, metabolic, and neurologic conditions (Table I) were evaluated for their association with death, as well as the individual binary variables. Stepwise logistic regression (entry *P* values of .25, *P* value to stay of .1) was used to facilitate and verify the final model selection of variables; however, statistical knowledge gained through separate analyses and clinical knowledge guided the selection

Table II. Patient disposition summary

	<i>N</i>	<i>Percent</i>
Enrolled	350	100.0
Reason excluded		
No operation	8	2.3
No DHCA	24	6.9
DHCA population	318	90.9
Not enrolled	123	100.0
Reason not enrolled		
Consent denied	57	46.3
Immediate operation	62	50.4
Immediate death	3	2.4
Other	1	0.8

process. Continuous variables that were strongly considered for model selection were also evaluated on the basis of quartiles. Strong statistical support and/or a clear clinical rationale for inclusion of variables into the final preoperative prediction model were required.

Model fit was determined by means of the Hosmer and Lemeshow⁸ method, and the deviance method was used for dispersion correction. The area under the receiver operating characteristic (ROC) curve is a measure of the overall prediction accuracy of the logistic model and, with its associated standard error,⁹⁻¹¹ was used to evaluate different models. The ROC curve is a graphic way of presenting separations

Table III. Demographic and selected preoperative characteristics (*N* = 318)

	<i>N</i>	<i>Percent</i>		
Sex				
Male	186	58.5		
Female	132	41.5		
Ethnicity				
White	242	76.1		
African American	46	14.5		
Hispanic	15	4.7		
Other	15	4.7		
Delivery room resuscitation	138	43.4		
Microcephaly	27	8.5		
Specific genetic syndrome	28	8.8		
Dysmorphism (no syndrome)	56	17.6		
		<i>Mean ± SD</i>	<i>Median</i>	<i>Q₁, Q₃</i>
Gestational age (wk)	318	38.5 ± 2.2	39.0	38, 40
Birth weight (kg)	309	3.1 ± 0.6	3.2	2.8, 3.6
Admission age (d)	318		2.0	1, 5
Apgar score at 1 min	301	7.5 ± 1.6	8.0	7, 8
Apgar score at 5 min	301	8.5 ± 1.1	9.0	8, 9
Hollingshead score	311	37.7 ± 17.3	39.0	27, 53

Q₁, Lower quartile (25%); *Q₃*, upper quartile (75%).

Table IV. Distribution of genetic syndromes (*N* = 318)

<i>Final diagnosis</i>	<i>N</i>	<i>Percent</i>
CHARGE	1	0.3
Goldenhar	3	0.9
Turner	2	0.6
VACTERL	4	1.3
Velocardiofacial	1	0.3
22q11 deletion	9	2.8
Dicentric 22	1	0.3
Trisomy 7	1	0.3
Trisomy 21	5	1.6
Trisomy 13	1	0.3
Total	28	8.8

CHARGE, Coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; **VACTERL**, vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects.

between two groups and is a plot of percent of deaths predicted to die versus percent of survivors predicted to die. This curve is generated by creating a frequency distribution of model-generated predicted probabilities and by using each of the observed predicted probabilities as a threshold for classification. For a given threshold value (predicted probability), all cases above the threshold are classified as a death, yielding the percent of those that died who were predicted to die and the percent of survivors predicted to die in survivors. Allowing the threshold to assume all observed predicted probabilities results in the ROC curve. The area under this curve is a measure of the probability that given a randomly

selected case from the survivor group (*N* = 266) and a randomly selected case from the death group (*N* = 52), the case from the death group will be assigned a higher predicted probability of death. This measure is independent of the prior probability of death and is considered to represent accuracy of the prediction model. The area is provided on the basis of the fitted model using all of the data and using an approximate jackknife¹² procedure, which provides predicted probabilities of death for each case, based on fitting the model with the remaining cases. The jackknife provides a conservative estimate of accuracy when using the same data set to create a model and estimate its accuracy. An exact logistic regression model was also fit to the preoperative variables.

The primary intent of the operative model was to evaluate the independent contribution of the duration of DHCA on death, adjusted for the variables in the preoperative model.

A risk stratification model was developed on the basis of the percent of deaths in each of the 18 (of a possible 24) unique combinations (profiles) of independent predictor variables represented in the preoperative logistic model. This model contains the information presented in the logistic model, but in a more clinically useful manner. The preoperative predictor variables will also be referred to as risk factors.

SAS (SAS Institute, Cary, NC) and LogXact (Cytel Software, Cambridge, Mass) software were used for all statistical analyses. All reported *P* values are 2-sided.

Results

Study population. A patient disposition summary is provided in Table II. A total of 350 infants were enrolled in the study from June 1992 until September

Table V. Distribution of cardiac defects, anatomic classification, and death by defect

Type of defect	Anatomic class	N	Percent	Death	
				N	Percent
HLHS	IV	131	41.2	35	26.7
Single ventricle	IV	40	12.6	7	17.5
Heterotaxy	III and IV	10	3.1	3	30.0
TGA/intact ventricular septum	I	36	11.3	0	0
TGA/VSD	I	13	4.1	0	0
TGA/VSD, CoAo	I	1	0.3	0	0
ToF alone	I	13	4.1	1	7.7
ToF/PA	I	11	3.5	0	0
ToF (other)	I	5	1.6	0	0
VSD/CoAo	II	12	3.8	1	8.3
VSD/interrupted aortic arch	II and III	14	4.4	1	7.1
VSD (other) [‡]	I, II, and III	9	2.8	1	11.1
Truncus arteriosus	I	7	2.2	0	0
TAPVR	I	6	1.9	0	0
Other	I, II, III, and IV	10	3.1	3	30.0
Total		318		52	16.4

HLHS, Hypoplastic left heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect; CoAo, coarctation of the aorta; ToF, tetralogy of Fallot; PA, pulmonary atresia; TAPVR, total anomalous pulmonary venous return.

[‡]Includes double-outlet right ventricle (n = 3), double-outlet left ventricle (n = 1), double-outlet right ventricle/subaortic stenosis/coarctation of the aorta (n = 1), and ventricular septal defect (n = 4).

Table VI. Intraoperative characteristics

	N	Mean ± SD
Surface cooling time (min) [*]	318	68.1 ± 20.5
CPB cooling time (min) [†]	318	11.8 ± 7.4
DHCA time (min)	318	53.7 ± 15.2
First CPB rewarming time (min) [‡]	318	27.3 ± 13.6
		Percent
Need for additional CPB [‡]	45	14.2
Modified ultrafiltration performed	77	24.2

^{*}Surface cooling time = ambient room temperature, cooling blanket, ice bags applied to head.

[†]Includes only the time the pump is running (excludes DHCA time).

[‡]Attempt to wean from CPB.

1997; however, 32 infants did not undergo surgery (n = 8) or DHCA (n = 24). Consequently, 318 infants were used to generate the risk model. There were 123 infants eligible for the study but not enrolled by reason of denied consent (57; 46%), surgery before the 16-hour preoperative treatment window (62; 50%), immediate death (3; 2%), and other reason (1; 0.8%). Mortality in eligible nonenrolled subjects was 25.2%.

Demographics and preoperative characteristics are provided in Table III. The study population was predominantly full term, appropriate weight for gestational age, and white. Apgar scores were available in 301 subjects, with mean values of 7.5 at 1 minute and 8.5 at 5 minutes, with 43% receiving some form of delivery room resuscitation other than simple tactile stimulation

Table VII. Day of death after surgery

Day of death	N	Percent
Day of surgery	19	36.5
Day after surgery	9	17.3
Day 3 through day 7	7	13.5
Day 8 through day 14	13	25.0
Day 15 through day 35	4	7.7
Total	52	100.0

and blow-by oxygen. Admission occurred at an average age of 5.6 days. Two hundred ninety-six (93.1%) of patients underwent surgery before 28 days after birth. Microcephaly occurred in 9%, dysmorphism in 18%, and definite genetic syndromes in 9% (Tables III and IV). The distribution of cardiac defects, their associated mortality, and anatomic classes are shown in Table V.

Intraoperative characteristics of the study population are provided in Table VI. The mean CPB cooling time was 11.8 minutes, mean DHCA time was 53.7 minutes, and mean duration of CPB rewarming was 27.3 minutes. Additional periods of CPB were used in 14% and modified ultrafiltration was performed in 24%.

Mortality. The overall mortality was 16.4% (52/318) and was unaffected by study year or investigational drug administration. Mortality was similar for classes III (25%; 2/8) and IV (25.6%; 46/180), which were therefore combined as a “single ventricle” group. Mortality in class I was 1% (1/102), in class II it was

Table VIII. Distribution of four identified preoperative characteristics

			Mortality	
Characteristics	N	%	N	%
Congenital heart disease classification				
Class I	102	32.1	1	1.0
Class II	28	8.8	3	10.7
Class III	8	2.5	2	25.0
Class IV	180	56.6	46	25.6
Genetic syndrome				
None	234	73.6	30	12.8
Dysmorphism	56	17.6	14	25.0
Genetic syndrome	28	8.8	8	28.6
Apgar score at 1 minute				
≤5	33	10.4	11	33.3
>5	285	89.6	41	14.4
Age at hospital admission (d)				
≤5	239	75.2	35	14.6
>5	79	24.8	17	21.5

Table IX. Risk of death based on the logistic regression model: Preoperative and operative

Model	Parameter estimate	Odds ratio		Odds ratio* (95% CI)	P value
		Asymptotic	Exact		
Preoperative model (prediction accuracy = 80%)					
Intercept	—5.6549				
Anatomy					
Class II	2.6896	14.7 [‡]	13.6 [‡]	1.6-134.0	.02
Class III + IV	4.1054	60.7 [‡]	53.5 [‡]	8.5-433.5	.0001
Genetic syndrome	1.8317	6.2 [§]	6.0 [§]	2.1-18.4	.001
Apgar score ≤ 5	1.3821	4.0	3.9	1.7-9.5	.002
Age at admission > 5 days	0.6547	1.9 [¶]	1.9 [¶]	1.0-3.8	.06
Operative model (prediction accuracy = 82%)					
Intercept	—5.9021				
Anatomy					
Class II	2.4580	11.7 [‡]		1.4-94.7	.02
Class III + IV	3.8075	45.0 [‡]		7.1-286.9	.0001
Genetic syndrome	1.7681	5.9 [§]		2.1-16.3	.001
Apgar score ≤ 5	1.2849	3.6		1.5-8.4	.003
Age at admission > 5 days	0.6958	2.0 [¶]		1.1-3.8	.03
DHCA time [‡]					
44 to 52 min	0.3063	1.4 [#]		0.5-3.9	.57
53 to 62 min	0.3894	1.5 [#]		0.6-4.0	.44
>62 min	1.0308	2.8 [#]		1.1-7.1	.03

*Wald confidence limits.

[†]DHCA time = duration of deep hypothermic circulatory arrest.[‡]Compared with class I anatomy.[§]Compared with no genetic syndrome.^{||}Compared with an Apgar score > 5.[¶]Compared with age at admission ≤ 5 days.[#]Compared with < 44 minutes.

10.7% (3/28), and in classes III and IV it was 25.5% (48/188). Death occurred rapidly in the study population (Table VII). All deaths occurred within 30 days of the operation except for one that occurred on day 35.

Logistic regression models. Four preoperative variables were significantly associated with death: anatomic classification, 1-minute Apgar score, genetic syndrome, and age at hospital admission. Table VIII

Fig 1. Preoperative risk-of-death logistic regression model ROC curve. Nonparametric area under ROC curve = 80%; standard error of the area = 2.8%.

provides the proportions of infants with these characteristics. The preoperative logistic model results (goodness of fit, $P = .9$) are presented in Table IX and the corresponding ROC curve is provided in Fig 1, which yields an accuracy of 80% (standard error of 2.8%). However, the accuracy of the jackknife ROC curve was 70%.

An operative risk-of-death model (goodness of fit, $P = .9$) was also developed (Table IX) to evaluate the independent contribution of DHCA duration. The 4th-quartile DHCA duration (>62 minutes) was associated with a significant increase in the odds of death (odds ratio [OR] = 2.8; $P = .03$). The accuracy (area under the ROC curve) increased to 82% (standard error of 2.7%) by including DHCA duration.

Fig 2 provides a clinically relevant risk stratification tree with 6 terminal nodes (N1 to N6) into which all 318 study subjects are assigned on the basis of the 4 preoperative variables. The lowest percentage of death (1%; 1/102) was in node N1, characterizing infants with class I anatomy. Class II anatomy defines node N2 with a 10.7% (3/28) mortality. Combined classes III and IV had the highest mortality (25.5%; 48/188). Within this group, a 1-minute Apgar score of 5 or less (node N3) was associated with a significantly increased

mortality (55.0%; 11/20) compared with those with higher Apgar scores (22.0%; 37/168). In node N4 the mortality for single ventricle infants with Apgar scores more than 5 and a genetic syndrome (55.6%; 5/9) was significantly higher than for those without a genetic diagnosis (20.1%; 32/159). Terminal nodes N5 and N6 show the effects of “age at admission” on infants with no genetic syndrome and an Apgar score more than 5. “Age at admission more than 5 days” was associated with higher mortality (31.6%; 12/38) than that of patients admitted before 5 days (16.5%; 20/121). Finally, survival of single ventricle infants with favorable Apgar scores, genetics, and admission age was 83.5%.

Another summary of the risk-of-death stratification is provided in Table X, with mortality risk ranging from 1.0% to 55%, depending on the CHD anatomic classification and the presence of risk factors.

Discussion

This study identified preoperative variables that were significantly associated with an increased risk of death after surgery. Death has always been intimately connected to the presence of CHD. Until recent decades, most severely affected infants with CHD died soon

Fig 2. Preoperative risk of death stratification model with associated model predicted probabilities of death. *P* represents the average of all node-predicted probabilities. *OR*, Odds ratio.

Table X. Preoperative risk of death stratification

Class	N	Deaths	Risk of death (%)	95% CI* (%)
I. Dual ventricle without arch repair	102	1	1.0	0.0-5.3
II. Dual ventricle with arch repair	28	3	10.7	2.3-28.2
III and IV. Single ventricle	188	48	25.5	19.5-32.4
3a. No risk factors†	121	20	16.5	10.4-24.4
3b. Greater than 5-day admission (only)	38	12	31.6	17.5-48.7
3c. Genetic syndrome or low Apgar score	29	16	55.2	35.7-73.6
3d. Any risk factor†	67	28	41.8	29.9-54.5

*Exact binomial.

†Risk factors are genetic syndrome, Apgar score < 5, and age at admission > 5 days.

after birth or survived tenuously with chronic cyanosis, congestive heart failure, failure to thrive, and psychomotor delay. With the development of the technology used in cardiothoracic surgery, much attention has been focused on innovative surgical techniques and refining neonatal CPB, DHCA, and modified ultrafiltration. The immediate modes of postoperative death are known and include myocardial failure, shock, hemorrhage, arrhythmias, systemic/pulmonary circulatory mismatch, and coronary artery insufficiency. However,

knowing the circumstances surrounding death does not allow preoperative risk stratification. The purpose of this investigation was to attempt to identify preoperative variables that may be associated with immediate postoperative death. Estimating the strength of these associations and creating a risk stratification model were additional objectives. These goals were chosen since relatively few studies have examined the pre-existing condition of infants before cardiac surgery,¹³⁻²⁰ and none has produced a risk-of-death prediction

model. Limperopoulos and associates¹³ reported the presence of microcephaly (occipitofrontal circumference < 3rd percentile) in 35.7% of 56 neonates before heart surgery and clinical neurologic abnormalities (eg, poor suck or low tone) in 28 of 50 (56%) infants examined. In the study by Newburger and colleagues,¹⁷ preoperative examinations showed definite clinical neurologic abnormalities in 55 of 152 (36.2%) infants before the operation. In the present study, infants frequently had low 1-minute Apgar scores, delivery room resuscitation, genetic syndromes, dysmorphic features, and microcephaly. Consequently, it is reasonable to seek clues regarding postoperative mortality among preoperative characteristics.

The mortality in this study (Table V) is comparable with that of other published series, ranging from 26% for single ventricle lesions, including hypoplastic left heart syndrome, to 3.2% for all other forms of complex neonatal heart disease.^{17,21,22} The proportion of deaths in the eligible, nonenrolled patients (25.2%) was significantly ($P = .01$) higher than that of enrolled infants (16.4%). This was attributed mostly to the urgent need for surgery and immediate death in over half of the nonenrolled infants (Table II).

Not surprisingly, cardiac anatomy was a powerful preoperative predictor of mortality. There are specific anatomic variants within diagnostic groups that increase mortality risk. Examples are hypoplastic left heart syndrome with intact atrial septum or transposition of the great arteries with intramural coronary arteries. This speculative risk model uses a broad anatomic and physiologic classification scheme that was simple and easy to apply to individuals or classes of infants with CHD.

The presence of a specific named genetic syndrome was the second most potent modulator of risk of death. Abnormalities of chromosome 22, reported with about 5% of CHD,²³ occurred in 3.5% (11/318) of study subjects. "Dysmorphism," present in 18% of other study infants, was also associated with a trend to increased risk of death ($OR = 1.963$; $P = .11$). This suggests that increased mortality risk is not confined to a single genetic condition but is associated with any dysmorphic or genetic condition. This agrees with Bove's observation²⁴ that mortality in patients with hypoplastic left heart syndrome was significantly increased by noncardiac congenital conditions.

Apgar scores can be lowered by asphyxia, sepsis, shock, CHD, medications, and neurologic disorders. Depressed 5-minute Apgar scores traditionally correlate with *morbidity* such as cerebral palsy.²⁵⁻²⁷ In this study, low 1-minute Apgar scores were present in 10%

of the population and were associated with increased mortality, perhaps indicating that the CHD prevented a smooth circulatory transition from intrauterine life or that the CHD had already introduced a neurologic disorder.

Older age at admission was associated with a higher risk of death ($OR = 1.9$; $P = .06$ in the preoperative model; $OR = 2.0$; $P = .03$ in the operative model). The influence of age at admission on mortality was independent of prostaglandin administration and other preoperative characteristics. The mechanism by which age at admission affects mortality risk is unknown.

This study has several important strengths. It is comprehensive in its scope of CHD, includes a wide range of anatomic lesions, and reflects the experience of four cardiothoracic surgeons over a 5-year period. It is intuitively appealing that cardiac anatomy, Apgar scores, and genetic syndromes could be associated with an increased risk of death. The relative joint contribution of each variable to mortality was quantified in terms of odds ratios and segments the population into subgroups of varying risks. This variation in risk is considerable. For example, survival of patients with single ventricle complex with favorable genetics, Apgar score, and age-at-admission status was 83.5% (Table X, 3a), compared with 44.8% (Table X, 3c) in high-risk patients. After adjustment for the predictive preoperative variables, the length of DHCA time was associated with mortality risk. Those infants requiring between 44 and 62 minutes of DHCA had an odds ratio of approximately 1.5, and those requiring more than 62 minutes had an odds ratio of 2.8, compared with infants needing less than 44 minutes of DHCA.

The study also has important limitations. The risk model reflects the population from which it was derived—a selected group of neonates who underwent heart surgery with DHCA after fulfilling specific inclusion criteria for the neuroprotection trial. Unknown patient selection biases may exist, and the distribution of CHD lesions in this group is heavily weighted to single ventricle complexes. Although internally consistent, the risk-of-death model is speculative, has not been validated on an independent population, and probably exaggerates its predictive abilities. With the use of the jackknife method of generating the predicted probability of death, the ROC curve was constructed to measure the potential over-optimism of the regression model, and the resulting prediction accuracy fell to 70%. Finally, great care should be exercised when considering the application of this information to an individual infant with CHD. The 95% confidence intervals show a substantial range of mortality risk values, espe-

cially in single ventricle lesions (Table X). Such information could be useful for counseling families of neonates awaiting heart surgery and for accommodating risk factors in future therapeutic interventional trials in this patient population.

In conclusion, it is important to acknowledge that the preoperative condition of these infants had a profound effect on survival. Potent predictors of mortality already exist before the operation commences.

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REFERENCES

- Benson D. Changing profile of congenital heart disease. *Pediatrics* 1989;83:790-1.
- Gillum RF. Epidemiology of congenital heart disease in the United States. *Am Heart J* 1994;127:919-27.
- Ferry P. Neurologic sequelae of cardiac surgery in children. *Am J Dis Child* 1987;141:309-12.
- Wells FC, Coghill S, Caplan HL, Lincoln C, Kirklin JW. Duration of circulatory arrest does influence the psychological development of children after cardiac operation in early life. *J Thorac Cardiovasc Surg* 1983;86:823-31.
- McConnell JR, Fleming WH, Chu WK, et al. Magnetic resonance imaging of the brain in infants and children before and after cardiac surgery. *Am J Dis Child* 1990;144:374-8.
- Hollingshead A. Four factor index of social status. New Haven [CT]: Department of Sociology, Yale University; 1975.
- Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley; 1989. p. 82-134.
- Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley; 1989. p. 135-73.
- Bamber D. The area above the ordinal dominance graph and the area below the receiver operating characteristic graph. *J Math Psychol* 1975;12:387-95.
- Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
- Goin JE, Preston DF, Gallagher JH, Wegst AV. Comparison of five digital scintigraphic display modes: an ROC curve analysis of detection performance. *Med Decis Making* 1983;3:215-27.
- SAS Institute Inc. SAS/STAT software: changes and enhancements through release 6.12. 1997. p. 461.
- Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics* 1999;103:402-8.
- Miller G, Eggli KD, Contant C, Baylen BG, Myers JL. Postoperative neurologic complications after open heart surgery on young infants. *Arch Pediatr Adolesc Med* 1995;149:764-8.
- Brunberg JA, Reilly EL, Doty DB. Central nervous system consequences in infants of cardiac surgery using deep hypothermia and circulatory arrest. *Circulation* 1974;49-50(Suppl):II60-6.
- Aisenberg RB, Rosenthal A, Nadas AS, Wolff PH. Developmental delay in infants with congenital heart: correlation with hypoxemia and congestive heart failure. *Pediatr Cardiol* 1982;3:133-7.
- Newburger J, Jonas R, Wernovsky G, et al. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. *N Engl J Med* 1993;329:1057-64.
- Blackwood MJA, Haka-Ikse K, Steward DJ. Developmental outcome in children undergoing surgery with profound hypothermia. *Anesthesiology* 1986;65:437-40.
- Majnemer A, Limperopoulos C, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status prior to and following open heart surgery in newborns and infants. *Circulation* 1997;96(Suppl):I130.
- Haneda K, Itoh T, Togo T, Ohmi M, Mohri H. Effects of cardiac surgery on intellectual function in infants and children. *Cardiovasc Surg* 1996;4:303-7.
- Bartram U, Grunenfelder J, Van Praagh R. Causes of death after the modified Norwood procedure: a study of 122 postmortem cases. *Ann Thorac Surg* 1997;64:1795-802.
- Kern JH, Hayes CJ, Michler RE, Gersony WM, Quaegebeur JM. Survival and risk factor analysis for the Norwood procedure for hypoplastic left heart syndrome. *Am J Cardiol* 1997;80:170-4.
- Glover TW. CATCHing a break on 22. *Nat Genet* 1995;10:257-8.
- Bove EL. Current status of staged reconstruction for hypoplastic left heart syndrome. *Pediatr Cardiol* 1998;19:308-15.
- American College of Obstetrics and Gynecology, Committee on Obstetric Practice. Fetal distress and birth asphyxia. Washington [DC]: American College of Obstetrics and Gynecology; 1994. Committee opinion no. 137.
- Nelson KB, Broman SH. Perinatal risk factors in children with serious motor and mental handicaps. *Ann Neurol* 1977;2:371-7.
- Ellenberg JH, Nelson KB. Cluster of perinatal events identifying infants at high risk for death or disability. *J Pediatr* 1988;113:546-52.

Discussion

Mr Marc R. de Leval (*London, United Kingdom*). I commend Dr Clancy and his colleagues for a well-conducted prospective study. The criteria of enrollment and the end points were well defined, and their very large data set was submitted to highly sophisticated statistical analysis. The demonstration that in a subset of high-risk patients, namely patients with a single ventricle, the strongest predictors of death were preoperative variables is extremely important. Traditionally, outcome analyses have concentrated on comparing intraoperative procedural variables, for example, DHCA, against hypothermic CPB, disregarding the preoperative variables. The objective of this study was to generate a prediction model of early deaths. The findings should help the authors to secure resources to extend similar studies to the late outcomes and to investigate the impact of those preoperative variables on late sequelae such as neurologic deficits and developmental delays.

I have two questions. You indicated that 123 patients did not fulfill the criteria of enrollment, and the mortality in that subset of patients was significantly higher than that in the patients you have analyzed. Is it conceivable that by excluding those patients you lost the opportunity to identify other predictors of death?

Second, I understand that the operations were performed by two surgeons doing the first phase of the study and two others doing the second phase of the study and that the results were similar for all those surgeons. Without trying to diminish the role of the surgeons, I would like to ask whether you believe that the system or the institutions in which they work is more important than the individual surgeons in the production of excellence?

Dr Clancy. I thank you for those comments, Mr de Leval. The first question concerned the effect of the nonenrolled patients. The children in the nonenrolled group who died were not predominantly the single ventricle patients but rather those who had something critical about their anatomy that precluded their waiting for 16 hours. The mortality in nonenrolled patients who would have been in classes III and IV was the same as that in the enrolled patients in classes III and IV. The differences really came out in the more critical cases. From that point of view, what would have otherwise been a lower mortality in classes I or II could have been raised. However, with class I used as the reference point, those differences would not have violated the broad categorizations.

Part of the difficulty is whether to be “lumpers” or “splitters.” I am sure that surgeons could give me, a neurologist, many examples of what should and should not be included in any one of these groups, but painting with a broad stroke kept this study fairly simple.

The second question concerns the importance of the surgeon versus the institution. We wanted to make a generalizable model, something that would not be institution-specific, predicting the results of a surgeon or a group of surgeons. However, the whole team really produces these results. For example, we have had the same cardiothoracic anesthesiologists at Children’s Hospital for the whole series, and I think that is part of the reason why these numbers are as good as they are. Whether this factor can be applied to another institution, I do not know. It is always tempting to think that one’s expertise is the reason for the good results, but much of what is going to happen to the patient is predetermined by the genetics and the condition of the child on admission to the hospital.

This is a speculative model derived from the data that we generated, so of course it fits our data. The question is whether it will hold up if we test it independently in another set of patients in another institution with different anesthesiologists and different surgeons. Testing this model on an independent data set of children is one of the jobs ahead of us. The reason it is consistent in our study is that it is derived from our own data.

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