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Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum

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Objective: We sought to define the prevalence of definitive end states and their determinants in children given a diagnosis of pulmonary atresia and intact ventricular septum during the neonatal period.

Methods: Between 1987 and 1997, 408 neonates with pulmonary atresia and intact ventricular septum were entered into a prospective study by 33 institutions. Competing risks analysis was used to demonstrate the prevalence of 6 end states. Factors predictive of attaining each end state were identified by means of multivariable analysis with bootstrap validation.

Results: Overall survival was 77% at 1 month, 70% at 6 months, 60% at 5 years, and 58% at 15 years. Prevalence of end states 15 years after entry were as follows: 2-ventricle repair, 33%; Fontan repair, 20%; 1.5-ventricle repair, 5%; heart transplant, 2%; death before reaching definitive repair, 38%; and alive without definitive repair, 2%. Patient-related factors discriminating among end states primarily included adequacy of right-sided heart structures, degree of aberration of coronary circulation, low birth weight, and tricuspid valve regurgitation. After adjusting for these factors, 2 institutions were predictive of 2-ventricle repair, 1 of Fontan repair, and 6 of death before definitive repair. Two institutions were predictive of both 2-ventricle and Fontan repair. These 2 institutions achieved a higher risk-adjusted prevalence of definitive repair and a lower prevalence of prerepair mortality.

Conclusions: Characteristics of neonates with pulmonary atresia and intact ventricular septum predict type of definitive repair. A morphologically driven institutional protocol emphasizing both 2-ventricle and Fontan pathways might mitigate the negative effect of unfavorable morphology. In the current era, 85% of neonates are likely to reach a definitive surgical end point, with 2-ventricle repair achieved in an estimated 50%.

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Read at the Eighty-third Annual Meeting of The American Association for Thoracic Surgery, Boston, Mass, May 4-7, 2003.

Received for publication May 9, 2003; revisions received Nov 11, 2003; accepted for publication Nov 17, 2003.

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J Thorac Cardiovasc Surg 2004;127:1000-8

0022-5223/$30.00

doi:10.1016/j.jtcvs.2003.11.057

Pulmonary atresia with intact ventricular septum (PAIVS) is characterized by the absence of communication between the right ventricle and the pulmonary trunk or the left ventricle. The lesion is morphologically heterogeneous, with varying degrees of right ventricular (RV) and tricuspid valve hypoplasia.[1] Aberrations of coronary circulation are common, ranging from cameral-coronary sinusoids and fistulas to right ventricle–dependent coronary circulation.[2]

TABLE 1. Morphologic characteristics in 334 neonates for whom an RV size score was assigned

RV size	n	% of 334	Tricuspid valve z score			RV-CA fistulas	RV-dependent coronary circulation
			Median	Range*	25th percentile		
−5 (severe hypoplasia)	62	19%	−2.3	−5.4 to 4.8	−3.3	35 (56%)	5 (8%)
−4	100	30%	−2.3	−5.3 to 0.6	−3.1	55 (55%)	10 (10%)
−3	79	24%	−1.1	−5.2 to 5.0	−1.9	28 (35%)	4 (14%)
−2	40	12%	−0.3	−3.1 to 3.2	−1.0	5 (13%)	0
−1	22	7%	0.4	−2.9 to 2.9	−1.2	3 (14%)	0
0 (normal for age)	16	5%	1.5	−1.6 to 5.0	0.6	0	0
≥1 (enlarged)	15	4%	2.4	−1.0 to 6.0	0.4	0	0

RV, Right ventricle/right ventricular; *CA,* coronary artery.
*High upper limits of tricuspid valve *z* score in neonates with a diminutive right ventricle are attributable to associated Ebstein's malformation.

A prior report from the Congenital Heart Surgeons Society (CHSS) examined various morphologic substrates and optimal initial palliative pathways for the initial 171 neonates enrolled with PAIVS.[3] Since that report, an additional 237 neonates were enrolled, and the present cohort includes all 408 neonates. We undertook this multi-institutional analysis to determine the proportion of neonates reaching defined end states, to identify factors predictive of each end state, and to synthesize these findings in a way that would reveal which factors are associated with a greater proportion of neonates reaching definitive repair.*

Patients and Methods

Patients

From January 1987 through April 1997, 408 neonates with PAIVS admitted to a CHSS institution within 30 days after birth were prospectively enrolled in a multi-institutional study. PAIVS was defined as no communication between the right ventricle and the pulmonary trunk and the absence of a ventricular septal defect, as determined on the basis of echocardiographic, catheterization, or surgical findings. Neonates were managed at 33 member institutions, with a median enrollment of 10 neonates per institution (range, 1-41 neonates). Mean birth weight was 3.1 ± 0.6 kg.

The median tricuspid valve *z* score was −1.2 (range, −5.4 to 6.0). Of 334 neonates for whom RV size was known, it was small for age in 303 (91%) and moderately or severely so in 49% (Table 1). tricuspid valve *z* score and RV size were moderately correlated ($r = 0.60$, $P < .001$). Right ventricle–coronary artery fistulas were present in 126 (31%). Right ventricle–dependent coronary circulation, defined as supply of a major portion of the left ventricle from only the right ventricle through a fistula or fistulas, was present in 19 (5%) neonates. Coronary aberrations were primarily associated with moderate or severe hypoplasia of right-sided heart structures.[3]

Morphology

Morphologic data were obtained by means of independent review of preintervention echocardiograms and catheterization results, as previously described.[3] A subjective grade for RV size was assigned on the basis of available combined information from catheterization, echocardiography, and surgical intervention. Normal-for-age cavity size was assigned a value of 0, extreme hypoplasia was assigned a value of −5, and intermediate degrees of hypoplasia were assigned values of −1 through −4. For enlargement, a similar scheme was used, with +5 denoting the most extreme enlargement.

Data Collection

Participation in the study and submission of patient information was voluntary and confidential. Parental consent was obtained consistent with individual institutional policies. Ethics approval for the CHSS Data Center is obtained annually from the Hospital for Sick Children in Toronto. Admission, diagnostic, interventional, and surgical records were abstracted into a database by CHSS members and staff.

Follow-up

The physician, family, or guardian of each child not known to have died has been contacted annually to ascertain clinical status and any intervening problems or procedures. After the most recent cross-sectional follow-up in 2002, current data (within 1 year of this analysis) were available for 373 (91%) children. For all neonates, follow-up time from the date of the first hospital admission was a median of 5.8 years (range, 1 day to 15.6 years). For surviving patients, median follow-up was 10.3 years (range, 1 day to 15.6 years). For neonates without current data (n = 35 [9%]), median follow-up was 3.4 years (range, 1 day to 9.1 years).

Data Analysis

All analyses were performed with SAS statistical software (version 8; SAS Institute, Inc, Cary, NC). Data are presented as frequencies, medians with ranges, or means ± SD as appropriate.

End states. Mutually exclusive end states were designated, including 2-ventricle repair, 1.5-ventricle repair (biventricular repair with superior cavopulmonary connection), 1-ventricle repair (completed Fontan operation with or without fenestration), primary heart transplantation, death before attaining a definitive repair, and survival without definitive repair. Definitive repair was defined as separation of systemic and pulmonary circulations (no extracardiac shunts and no intracardiac right-to-left shunts at the

*A preliminary analysis of end states in 346 neonates was presented by E. H. Blackstone, J. W. Kirklin, and F. L. Hanley at 69th Scientific Session, American Heart Association, November 1996.

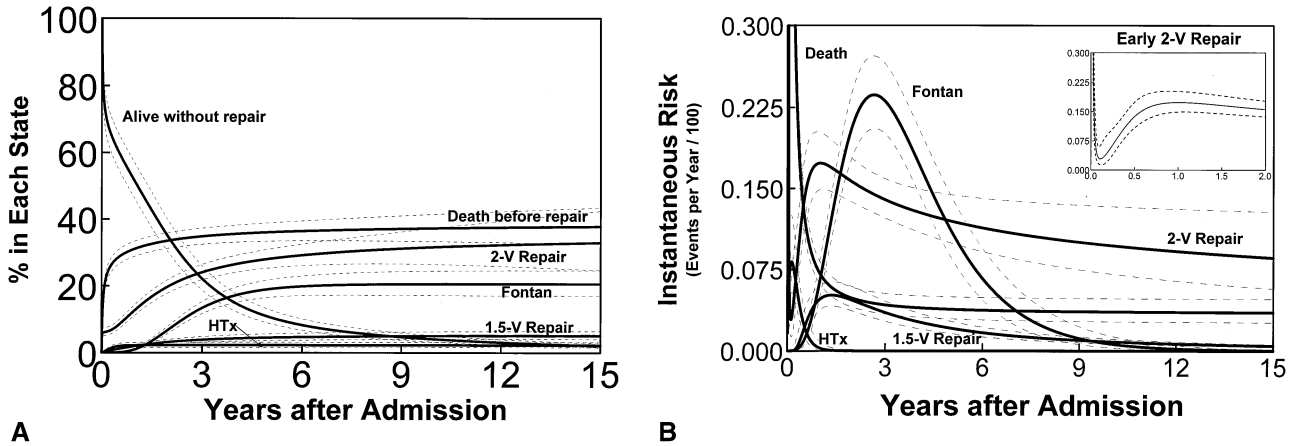

Figure 1. Non–risk-adjusted competing-risks depiction of end states in 408 neonates with PAIVS. A, Proportion of children reaching each end state over time after initial hospital admission. All patients begin alive at the time of initial admission (time = 0) and thereafter migrate to an end state at a time-dependent rate defined by the hazard functions. At any point in time, the sum of the proportion of children in each state is 100%. For example, at 5 years, the estimated prevalences of end states are as follows: 2-ventricle repair, 28%; Fontan operation, 19%; 1.5-ventricle repair, 5%; cardiac transplantation, 2%; death before reaching a repair state, 36%; and alive without end state, 11%. *Solid lines* represent parametric estimates (surrounded by their 70% confidence intervals in *dashed lines*) of the accumulative effect of each hazard function applicable to patients remaining alive without a definitive repair at each point in time. B, Parametric hazard functions *(solid curves)* with 70% confidence intervals *(dashed curves)* representing the instantaneous risk of attaining each of 5 end states at any given time up to 15 years after initial admission. For clarity, the *inset* expands the 2-ventricle hazard function.

atrial level), such that children undergoing fenestrated 2-ventricle repair were not considered definitively repaired until the intra-atrial shunt was known to be closed, either surgically or spontaneously.[3]

Prevalence of end states. Non–risk-adjusted freedom from each state was estimated nonparametrically by using the Kaplan-Meier method. Rates of transition from the initial state of mixed circulation to each competing end state was estimated by means of hazard-function multiphase parametric modeling.[4] By using competing-risks methodology, the individual hazard functions were integrated to yield the actual proportion of neonates reaching each defined end state at any given time after initial hospital admission.[5]

Risk factors for end states. Demographic and morphologic factors associated with each end state were sought by using multivariable regression of hazard models. Variable selection was primarily performed by means of bootstrap bagging.[6] For the bootstrap step, randomly selected data sets (n = 200) of the same size as the original data set were analyzed by means of automated stepwise regression, with an inclusion criterion of a *P* value of .05 or less. For the aggregation step, cluster analysis was used to identify risk factors occurring in 50% or more of the analyses, with the most commonly occurring transformation (if applicable) selected. These factors were entered into a final model, and those with *P* values of .05 or less were retained. Frequency of identifying factors (reliability) according to bagging is reported. Parameter estimates signify contribution of a variable to the overall model, and their interpretation is affected by increments of measurement and, where applicable, mathematic transformations.

Effect of institution. After adjusting for retained patient factors, institutions associated with each end state were identified in a similar manner. The competing-risks model containing patient factors was repeated, entering each institution identified as a risk factor for 2-ventricle repair, for the Fontan operation, and for death before definitive repair to further assess institutional outcomes. Adjusting outcomes for each institution on the basis of neonates managed in it allows comparison among institutions in a risk-adjusted manner. Nomograms of individual institutional outcomes on the basis of the morphologic spectrum (tricuspid valve *z* score with concordant RV size adjustment) of PAIVS were constructed.

Results

For all 408 neonates, survival at 1 month, 6 months, 1 year, 5 years, and 15 years after initial admission was 80%, 70%, 68%, 60%, and 58%, respectively. Risk factors for death at any time were similar to those described below. There was improvement in overall survival across the study period. Holding other factors constant, predicted 5-year overall survival for neonates enrolled in 1987, 1992, and 1997 was 49%, 63%, and 79%, respectively.

Prevalence, Timing, and Factors Predictive of End States

Prevalence of neonates reaching a definitive end state was 49%, 89%, 96%, and 98% at 1, 5, 10, and 15 years after initial hospital admission, respectively (Figure 1, *A*). Instantaneous rates of reaching each end state at any given time after entry are shown in Figure 1, *B*. Incremental risk factors for each end state are shown in Table 2.

TABLE 2. Incremental factors associated with reaching each of 5 defined end-states in 408 neonates with pulmonary atresia with intact ventricular septum

Factor	Parameter estimate ± SE	*P* value	Reliability (%)
2-ventricle repair			
Early phase			
RV size* closer to normal	0.32 ± 0.08	<.001	99
TV *z* score closer to normal (per 1 SD)	0.27 ± 0.12	.026	54
Higher LV pulse pressure (per 5 mm Hg)	0.26 ± 0.11	.020	55
Institution E	1.28 ± 0.64	.044	56
Late phase			
Lesser degree of RV-CA fistula(s)†	0.62 ± 0.18	<.001	95
TV Z score‡ closer to normal (per 1 SD)	2.79 ± 0.94	.003	75
RV size* closer to normal	0.25 ± 0.10	.014	72
Higher birth weight (per 1 kg)	0.51 ± 0.25	.042	56
Institution M	1.74 ± 0.63	.007	78
Institution B	0.91 ± 0.44	.040	54
Institution L	1.79 ± 0.54	<.001	70
Institution E	0.84 ± 0.41	.042	52
1.5-ventricle repair			
Early phase			
Higher RV systolic pressure (per 10 mm Hg)	0.31 ± 0.11	.007	60
TV *z* score closer to normal (per 1 SD)	0.32 ± 0.12	.010	73
Institution G	2.62 ± 0.61	<.001	86
Institution A	2.10 ± 0.72	.004	84
1-ventricle repair			
Early phase			
Lower TV *z* score‡	4.00 ± 0.92	<.001	91
Institution T	1.94 ± 0.36	<.001	97
Institution E	2.38 ± 0.51	<.001	90
Institution M	1.47 ± 0.53	.006	83
Heart transplantation			
Early phase			
Later date of admission (per 1 y)	0.42 ± 0.13	.002	93
Institution R	2.61 ± 0.80	.002	72
Death before attaining definitive repair			
Early phase			
Lower birth weight§	4.32 ± 1.18	<.001	84
Severe TV incompetence	1.47 ± 0.28	<.001	90
Lower (and higher) TV *z* score	0.28 ± 0.08	<.001	75
Enlarged RV	1.31 ± 0.32	<.001	75
Institution Y	1.26 ± 0.33	<.001	91
Institution D	1.23 ± 0.46	.008	66
Institution H	1.44 ± 0.40	<.001	86
Institution S	0.90 ± 0.29	.003	83
Late phase			
Lower RV:LV systolic pressure ratio‖	0.87 ± 0.35	.014	81
Prior balloon atrial septostomy	1.41 ± 0.52	.007	50
Earlier date of admission¶ (per 1 y)	1.00 ± 0.27	.001	63
Institution C	2.06 ± 0.65	.002	71
Institution P	2.01 ± 0.78	.010	58

TV, Tricuspid valve; *RV,* right ventricle/right ventricular; *LV,* left ventricle; *CA,* coronary artery.
*Grade of RV size entered after square transformation.
†Graded spectrum ranging from no fistulas to fistulas with severe RV-dependent coronary circulation.
‡Entered after exponential transformation.
§Entered after inverse transformation.
‖Entered after square transformation.
¶Measured as time since October 1, 1987: entered after logarithmic transformation.

Completed 2-ventricle repair (n = 120). The prevalence of completed 2-ventricle repair was 13%, 28%, and 33% at 1, 5, and 15 years after admission, respectively. The instantaneous rate revealed 2 major phases. An early phase, starting near the time of admission and extending to 3 months, represented 25 neonates with favorable morphology. The

subsequent late hazard phase included 95 children, increased beyond 2 months, and spans the remainder of the study period. It corresponds to the wide time frame for closing extracardiac and intra-cardiac shunts.

Fontan operation (n = 76). The prevalence of Fontan repair was 1%, 19%, and 20% at 1, 5, and 15 years after admission, respectively. There is a single hazard phase for the Fontan operation peaking at 3 years.

Other definitive repairs (n = 31). The 15-year prevalence of 1.5-ventricle repair and cardiac transplantation was 5% and 2%, respectively.

Death before definitive repair (n = 149). The prevalence of death before definitive repair was 31%, 36%, and 38% at 1, 5, and 15 years after admission, respectively, and was heavily concentrated around the time of first admission. For neonates not reaching a definitive repair within the first 2 years of life, there was an ongoing late hazard for death.

Predicted Pathway

From patient factors in Table 2, predicted 1- or 2-ventricle pathway was determined for each neonate. The 2-ventricle pathway was predicted for 246 (60%) neonates, and the 1-ventricle pathway was predicted for 162 (40%) neonates. The management protocol matched the predicted protocol in 315 (77%) neonates. An increased prevalence of death before reaching definitive repair was observed for neonates managed differently from the predicted pathway (54% vs 31%, $P < .001$).

Effect of Institution

A competing-risks model was constructed for each institution identified as a risk factor for one or more end states. Nomograms illustrating the risk-adjusted 5-year prevalence of end states for representative institutions favoring 2-ventricle, Fontan, and both 2-ventricle and Fontan pathways are shown in Figure 2. Institutions favoring 2-ventricle repair on average achieved a higher prevalence of 2-ventricle repair at a cost of higher prerepair mortality (Table 3). Such institutions might improve outcomes through more aggressive application of the Fontan pathway in children with less favorable morphology (Figure 2, *A*).

The single institution favoring Fontan repair achieved good survival at the cost of fewer 2-ventricle repairs, even for more favorable morphology (Table 3). Such institutions might improve outcomes by applying 2-ventricle repair to children with favorable morphology (Figure 2, *B*).

Two institutions applied both 2-ventricle and Fontan pathways in a morphologically dependent manner (Figure 2, *D*) to achieve comparably excellent survival and higher prevalence of 2-ventricle and Fontan repairs, with few remaining unrepaired at 5 years (Table 3).

High-risk institutions, with the exception of institution H, demonstrated a reticence toward committing to either a 2-ventricle or Fontan pathway, as indicated by the high prevalence of children alive without a definitive repair at 5 years compared with numbers in low-risk-factor institutions (Figure 2, *C*).

Discussion

PAIVS is a rare lesion, and most previous reports include small numbers of children treated at a single institution.[7-13] A unique aspect of our study made possible by the large unselected population of neonates accrued by CHSS institutions is consideration of various mutually exclusive end states achieved in these neonates. By accounting for multiple simultaneous outcome events, competing risks methods allow determination of the actual prevalence of each end state over time after entry, multivariable definition of patient-related factors associated with the distribution of end states, and demonstration of the risk-adjusted effect of institution on the prevalence of end states.

Although variable, reported survival in neonates with PAIVS has improved over time. In an earlier era, reported 5-year survival among 135 neonates admitted between 1970 and 1989 was less than 50%, with 25% of children determined to be suitable for definitive repair.[14] The overall 5-year survival in our multi-institutional study was 60%, with adjusted 5-year mortality for neonates admitted in later years of 79%. The proportion reaching definitive repair at 5 years was 52%. Our data are similar to those of a national Swedish study of 84 children born between 1980 and 1999.[15] Several recent reports have documented outstanding survival, ranging from 76% to 98% at 5 years.[9,12,13] Despite excellent survival, the proportion undergoing definitive repair in these studies was 55% to 72%.

The morphologic spectrum of PAIVS requires different management protocols with the goal of maximizing the number of neonates reaching appropriate definitive repair. From the institutional findings of this study, we infer that surgical protocol on the basis of individual risk factors present might optimize outcomes. Findings of this and the initial CHSS study show that the decision process must begin at the time of initial admission.[3]

Our study demonstrates that an optimal protocol emphasizes the 2-ventricle pathway for favorable morphology and the Fontan pathway for unfavorable morphology. Such a protocol results in a higher proportion of neonates reaching a definitive repair, earlier completion of definitive repair, and a lower proportion of prerepair attrition. We have shown that such a protocol at least in part mitigates the negative effect of hypoplastic right-sided heart structures on survival. Selecting a Fontan pathway for children with marginal or severe anatomy should not be considered a failure of therapy.[11,16] The benefits of selective management are supported by several previous reports.[12,13]

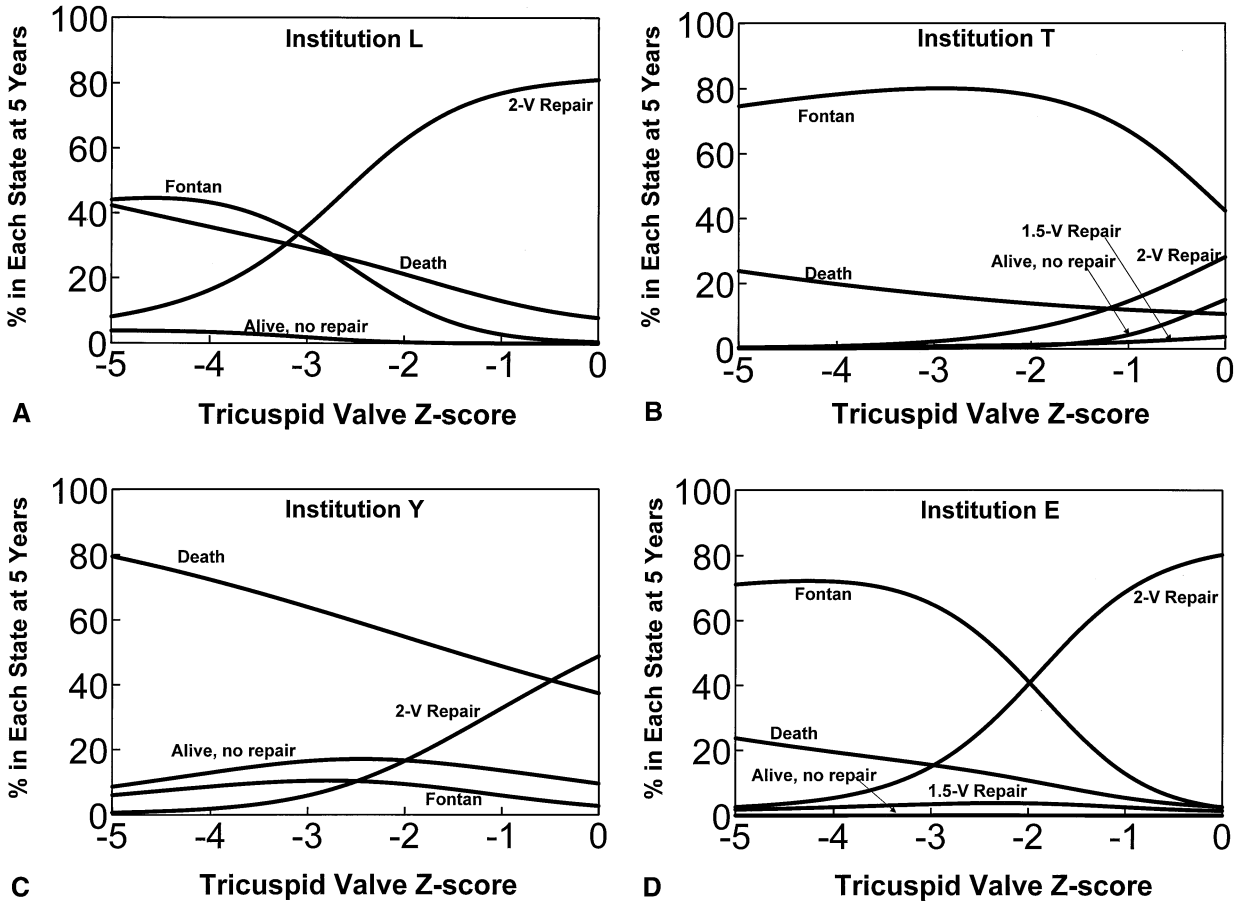

Figure 2. Risk-adjusted competing-risks nomograms for individual institutions on the basis of morphologic spectrum of PAIVS. The predicted 5-year prevalences of end states *(vertical axis)* are plotted against tricuspid valve *z* scores with commensurate adjustment of RV size. All other predictors are set to their median value. A, Institution L favored 2-ventricle repair. For favorable morphology, a high proportion of 2-ventricle repairs is achieved. For unfavorable morphology, the rate of Fontan operation is comparably low, mortality is high, and a small proportion of patients remain alive without definitive repair. B, Institution T favored the Fontan operation for most morphology. In exchange for a small proportion of neonates with favorable morphology receiving a 2-ventricle repair, the institution achieved a low rate of mortality, particularly for severe morphology. C, Institution Y was a high-risk institution for death. The large proportion remaining alive at 5 years without definitive repair indicates that it favored neither a 2-ventricle nor Fontan pathway. D, Institution E favored both 2-ventricle and Fontan pathways. For severe morphology, a large proportion of neonates undergo the Fontan operation. For favorable morphology, a large proportion undergo 2-ventricle repair. Across the morphologic spectrum, the mortality rate is comparably low, and essentially, all children have had a definitive repair at 5 years.

The method of risk adjustment warrants further explanation. Multivariable analysis of patient factors identified important variables in predicting the prevalence of each end state, with the weight of each factor determined from the overall data. In contrast to risk stratification, institutions associated with a comparably high prevalence of one or more end states were identified after adjusting for important patient variables (ie, institutions predisposed to a particular end state after consideration of their patient population). The method allows fair comparison of outcomes from different institutions on the basis of different levels of risk managed by each institution.

Several findings of the study deserve comment. Although we and others have shown that tricuspid valve size is a primary determinant of type of repair, our analysis reveals that there are other variables to be considered. We demonstrated that both tricuspid valve *z* score and RV size are important determinants of achieving a 2-ventricle repair, either early or late. Because tricuspid valve diameter and RV size were only moderately correlated, the inference is

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TABLE 3. Five-year prevalence of end-states for each risk factor institution.

			Mean ± SD predicted 5-year prevalence				
Institution	n	High-prevalence states	2-V repair	Fontan	1.5-V repair	Death before repair	Alive without repair
Institution E	20	2-V, Fontan	36% ± 28%	48% ± 26%	3% ± 1%	13% ± 7%	—
Institution M	9	2-V, Fontan	56% ± 29%	39% ± 31%	—	3% ± 1%	1% ± 1%
Institution T	19	Fontan	8% ± 8%	73% ± 10%	1% ± 1%	16% ± 4%	2% ± 4%
Institution L	14	2-V	47% ± 27%	23% ± 17%	—	25% ± 11%	2% ± 2%
Institution B	13	2-V	35% ± 23%	17% ± 9%	4% ± 1%	37% ± 10%	7% ± 5%
Institution Y	27	Death	17% ± 15%	9% ± 2%	—	59% ± 13%	15% ± 3%
Institution H	17	Death	25% ± 24%	14% ± 2%	—	54% ± 21%	—
Institution D	11	Death	28% ± 25%	18% ± 9%	—	41% ± 17%	10% ± 4%
Institution S	41	Death	18% ± 17%	19% ± 6%	1% ± 0%	47% ± 12%	13% ± 2%
Institution P	10	Death	19% ± 15%	—	—	24% ± 6%	57% ± 10%

Percentage value represents the predicted prevalence of each end-state averaged across the spectrum of *z* scores from −5 to 0. RV size was adjusted commensurate with TV *z* score, with all other predictors set at median value and held constant for all institutions. *2-V,* Completed 2-ventricle repair; *1.5-V,* 1.5-ventricle repair.

that adequacy of both structures be considered when determining candidacy for 2-ventricle repair.[10] In addition to tricuspid valve size, tricuspid valve morphology is an important factor determining suitability for 2-ventricle repair.[17] Surrogated by RV enlargement and severe tricuspid regurgitation in this study, associated Ebstein's malformation imposes a high risk of death and not achieving 2-ventricle repair. There are instances in which the size of the right ventricle and tricuspid valve suggest potential for 2-ventricle repair, but tricuspid valve dysplasia precludes reaching that outcome. Additionally, valves with an acceptable *z* score might have stenotic dysplasia, with thickened knobby leaflets and abnormal chordal attachments making them irreparable. Because tricuspid valve replacement in young children is undesirable, valve closure (often with a patch) and proceeding to the Fontan operation might be the best option.

We did not find aberrations of coronary circulation to be specific risk factors for death, a finding supported by other studies.[12,13] When considered in the context of improving overall survival, this finding lends further evidence that the most unfavorable morphologic subsets of neonates with PAIVS can be managed successfully. Because multiple patient-related factors determine the appropriate protocol, management decisions should be made after careful delineation of presenting characteristics for each neonate.

In conclusion, we observed improving overall survival across the span of the study. Furthermore, we estimate that definitive repair could be achieved in 85% of neonates within 3 to 5 years after admission. On the basis of factors predicting repair pathway, we expect that 50% of neonates will be suitable for 2-ventricle repair, and 35% will be more appropriately managed on a Fontan pathway.

We thank all the CHSS members and their colleagues in pediatric cardiology for their contributions to the study and the Data Center staff (Geraldine Cullen-Dean, Olga Levesque, and Sally Cai) and institutional coordinators for collecting information and following children. Also acknowledged are the contributions of Drs R. M. Freedom, N. C. Nanda, and J. W. Kirklin in detailing and recording morphologic data. Dr. Ashburn gratefully acknowledges the financial support of the Bradshaw Fellowship in Surgical Research from Wake Forest University School of Medicine.

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Discussion

Dr Roger B. B. Mee *(Cleveland, Ohio)*. Dr Ashburn, I understand that you are in the middle of a general surgical residency. Your grasp of this complex subject and your presentation was outstanding. I hope you choose to do congenital heart surgery.

In this study sophisticated statistical methods have been used to tease out factors predisposing to the 6 end points: biventricular repair, Fontan 1.5-ventricle repair, heart transplantation, death, or still awaiting definitive repair. The performance of each of the 33 institutions has been analyzed, its cohort has been adjusted for end-point risk factors, and an attempt has been made to define pulmonary atresia–intact ventricular septum management strategy.

The overall mortality for the 408 patients from the period from 1987 through 1997, which was firmly within the modern era of neonatal surgery, is disappointing—40% at 5 years—and overwhelmingly clustered around neonatal palliation. There was a huge mortality spread of 15% to 59% among institutions, and this mortality was not related to volume, which I think is interesting.

A management strategy biased toward biventricular repair increased the probability of achieving that end point but also increased the possibility of death, and a bias toward a Fontan track increased the probability of that end point and reduced the risk of death.

The study's conclusion was that with appropriate end-point strategies, 85% of the cohort should have achieved repair end points by 3 to 5 years, in particular 40% biventricular repair and 35% Fontan repair. Interestingly, these idealized end points are identical to those reported in 1986 (reference 7 in the manuscript) for a series of 48 patients in whom management strategy was based simply on the presence or absence of a well-formed infundibulum.

From the database, identified risk factors for mortality before definitive repair could be clustered into 2 groups: group A, very small right ventricle and tricuspid valve, and right ventricle–dependent coronary circulation, all of which are strongly related; group B, very large right ventricle and tricuspid valve, low RV pressure, severe tricuspid regurgitation, Ebstein's anomaly, low birth weight, and associated noncardiac abnormalities, including hypoplastic lungs. With the 1997 cutoff, nearly all interventions were surgical. In fact, I think if neonatal intervention was confined to the catheter laboratory, most of those patients would not be included because they would not be in our surgical databases.

I have 4 questions. If Ebstein's anomaly requiring neonatal surgical intervention was removed from the database, would this eliminate or soften my group B risk factors for death?

Second, can the database explain why some high-volume institutions had such high mortality?

Would it be possible to confirm from the current database that the presence or absence of a well-formed infundibulum strongly confers a large right ventricle and tricuspid valve, a very low incidence of RV to coronary fistulas, and a virtual absence of right ventricle–dependent coronary circulation and that an absent infundibulum confers a very small right ventricle and tricuspid valve and a high incidence of RV to coronary fistulas and includes all cases of coronary stenosis and obstructions and right ventricle–dependent coronary circulation and that this single factor would just as accurately predict the idealized repair pathways that are the conclusion of this study?

Finally, do you think it would now be appropriate and worthwhile to ask the contributing 33 institutions to supply data on all neonates with neonatal interventions confined to the catheter laboratory and to ascertain whether this approach represents an advance in terms of mortality and in achieving predicted end points?

Dr Ashburn. Thank you, Dr Mee. In regard to the first question asking about the inclusion or exclusion of patients with associated Ebstein's malformation of the tricuspid valve, I do not think that excluding those patients from this analysis would affect the risk factors that we identified, nor do I believe that they would "soften," as you say, the group A or group B risk factors. The reason I say that is because although Ebstein's anomaly was not specifically identified as a risk factor, there are at least 3 variables in the risk factors that are surrogates for Ebstein's anomaly.

There were 20 patients with Ebstein's anomaly, and half had RV enlargement and another half had severe tricuspid regurgitation. I think that these risk factors are in the analysis that Ebstein's anomaly is actually surrogated for. Therefore these patients with Ebstein's anomaly, on the basis of their other characteristics, would be expected to have a high risk of death, which is actually seen.

In regard to the second question, why high-volume institutions have a high risk of death, I cannot answer that specifically. What I can say is that we adjusted institutional risk factors for patient characteristics that were seen by that institution. Therefore I do not believe that it is caused by differences in the patient population that those institutions are seeing.

On the other hand, we do have data, and we showed a trend in treating patients in a way that is concordant with their predicted ultimate end point, and we were able to show that the institutions that have improved outcomes are treating their patients in a more concordant manner; that is, the management pathway matches more often the predicted ultimate end point.

In regard to your third question, I know that your paper from 1986 showed that the status of the RV infundibulum is an excellent predictor of the end state that a neonate can reach. Unfortunately, our database does not have that specific piece of information in it. The morphologic data were obtained by means of blinded independent review done by 3 cardiologists looking at all catheterizations. I think it is logical to infer that a larger tricuspid valve size and a larger right ventricle, as we have in our analysis and in our risk factor set, probably does correlate to a better infundibulum, but I do not have the data to show that.

In regard to your last question about retrospective enrollment of neonates who underwent an initial interventional procedure, there

were only 9 patients in the database who had that. Of those 9 patients, 7 had a biventricular repair, but I would also add that all patients who ended up with a biventricular repair after an interventional procedure also had a shunt during the first admission.

I think that the current status of catheter intervention is different than what we were seeing in the period of this study. Whether enrolling patients retrospectively during that same time point now would give us the data that we are looking for to compare catheter intervention with surgical intervention, I am just not sure that it would answer the specific questions we are looking for because interventional procedures have changed so much, and I think their outcomes have changed also.

Dr John E. Foker *(Minneapolis, Minn)*. You have again confirmed that the results are poor for infants with PAIVS, the mortality is high (40% at 5 years), and only 31% of survivors had a 2-ventricle repair. The biggest source of difficulty is with those who have very small right-sided hearts. We believe that the best way to significantly improve these results will be to induce growth of the hypoplastic ventricles. Induced growth will produce better short-term and long-term results than will improved selection of which patients should have 1-ventricle, rather than 2-ventricle, repairs. Therefore the basic questions are as follows: Does an adequate growth potential exist for these hypoplastic right-sided hearts regardless of morphology, and can growth be relatively rapidly induced?

Our hypothesis is that this is not a gene-level defect, and the growth potential does exist. As we have shown, growth will be induced by increased flow across the tricuspid valve. Therefore after one relieves the RV obstruction, a mildly restrictive atrial septal defect (gradient of 6 mm Hg) will encourage tricuspid flow and yet allow sufficient right-to-left shunting for an adequate cardiac output. In the interim pulmonary blood flow is preserved by prostaglandin E1 infusion or, for very small right ventricles, a shunt. The coronary-to-RV connections can be easily taken down off bypass.

Our data indicate that all of these right ventricles will grow, usually within days or weeks, even those with z values as low as -9. Catch-up growth clearly occurred. An infundibulum did not seem to be necessary for adequate growth. Importantly, the tricuspid valves will also grow. The valves of 10 patients have been analyzed. With an average beginning tricuspid z value of -4, these valves grew to an average value of -1. About 25% to 30% of the smaller valves will have some degree of commissural fusion apparent after growth. Significant stenoses will require balloon or open valvotomy. Overall, our mortality is much lower (18% at 5 years), and very importantly, all located survivors had 2-ventricle repairs.

My question is, have you analyzed your patients to establish the growth potential of the right ventricle and tricuspid valves in those infants who have had the outflow obstruction relieved? It has frequently been stated that the ventricles and valves will not grow adequately, and this belief turns therapy away from a 2-ventricle repair. Our data clearly dispute this conclusion and approach. Because the growth potential is such an important question, it would seem that an analysis of your patients could provide this vital answer.

Dr Ashburn. Thank you. We have not looked at repeated measures of RV size and tricuspid valve size, and in response, I would just state that I do not know of any literature that specifically shows that the right ventricle or tricuspid valve grow disproportionately to somatic growth. In other words, certainly the right ventricle and tricuspid valve might grow in relation to body growth, but there is no so-called catch-up period, and I am just not aware of literature showing that. But I think your point is well taken that this would represent a good population to look at repeated measures of RV size and tricuspid valve size to assess right-sided heart growth capabilities.