Outcome of preterm infants with congenital heart disease

Ellen Dees, MD, Hwei Lin, MD, Robert B. Cotton, MD, Thomas P. Graham, MD, and Debra A. Dodd, MD

Objectives and study design: To evaluate the morbidity and mortality of preterm infants with congenital heart disease (CHD), a chart review was performed for infants with CHD, excluding isolated patent ductus arteriosus, who were <37 weeks’ gestation, weighed <2500 g, and were admitted to our neonatal intensive care unit from 1976 to 1999 (N = 201).

Results: Patients in the study represented 1.9% of the total neonatal intensive care unit population <37 weeks’ gestation and <2500 g. The median gestational age was 33 weeks, and the mean birth weight was 1852 g. CHD diagnosis frequencies were similar to those reported in other large incidence studies, except for a higher percentage of conotruncal defects. The risk of necrotizing enterocolitis was 1.7 times higher and the overall mortality twice as high in our patients compared with patients in the neonatal intensive care unit who did not have CHD. Cardiac surgery (n = 133) was performed on 108 patients. During the recent period of 1985 to 1999, compared with our institution’s overall results for CHD surgery, the operative mortality rate was 10.4% versus 5.4% for closed procedures and 25.4% versus 10.5% for open procedures. The actuarial survival rate is 51% at 10 years; survival improved as the study period progressed.

Conclusions: Infants with both CHD and prematurity did significantly worse than either group alone. Such outcome data are required for proper allocation of resources to care for this high-risk pediatric population.

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Preterm infants with congenital heart disease have special challenges of diagnosis and treatment; with continued advances in neonatology, this population can be expected to grow in numbers and in demand for medical resources. Heat lability, vulnerability to infection, limited hemodynamic reserve, and immaturity of organ systems, particularly cardiac muscle, lung, and liver, are factors that make the perinatal transition period more difficult for the preterm than the term neonate. The addition of CHD complicates this process significantly. For example, the pulmonary vasculature in preterm infants is known to be less well muscularized than in term infants. This condition may leave the preterm infant vulnerable to congestive heart failure from left to right shunt lesions such as ventricular septal defects at an earlier age, that is, within days or weeks after birth rather than weeks or months. Care of CHD has moved toward early primary repair rather than staged repair, with a palliative operation as the first step. The extension of primary repair to preterm infants has been advocated, but the limits of this proposal in terms of size and gestational age have not been studied.

METHODS

The study design was a retrospective chart review covering a period of 23 years. Patients were identified through a computer database maintained on all neonatal intensive care unit admissions. The database includes demographic information and admitting diagnosis and is updated continually, with additional diagnoses made during the hospitalization of each patient.

Eligibility criteria for inclusion in the study group were gestational age <37 weeks, birth weight <2500 g, and a di-
Diagnoses of CHD made while the infant was in the NICU. The study period was 23 years, from July 1976 to May 1999. Patients with a diagnosis of isolated patent ductus arteriosus were the only exclusion. Vanderbilt is a referral center for CHD for most of the state of Tennessee and portions of several neighboring states. Otherwise healthy preterm infants may be hospitalized at a number of other hospitals in the region. Thus our data are not intended to accurately represent incidence data for CHD in our region.

Diagnoses of CHD were made on the basis of physical examination, history, chest x-ray evaluation, echocardiography, cardiac catheterization, operative findings, and autopsy. Diagnosis of necrotizing enterocolitis was made at clinical evaluation in patients with (1) signs of abdominal distension or guaiac positive stools, (2) x-ray findings consistent with NEC, and (3) management changes to include temporary stopping of feedings and a course of antibiotics. Intraventricular hemorrhage was diagnosed and graded on the basis of head ultrasonography. Further data were gathered on each patient from hospital chart review and contact by phone, letter, or both with the follow-up physician. Statistical significance was determined with \( \chi^2 \) Fisher’s Exact analysis or Student’s \( t \) test where appropriate; significance was defined as \( P \leq .05 \). Kaplan-Meyer survival curves were generated with age of death or age at last follow-up visit used as end points.

The comparison group was the July 1976 to May 1999 NICU population, as identified from the database, that met all of the study criteria except a diagnosis of CHD (\( n = 10,476 \)). For surgical outcomes the comparison group was all infants <1 year of age who underwent open or closed heart surgery for a congenital heart lesion, excluding the patients in the study (\( n = 2966 \)). Because our surgical database is only current from 1985, the study group was also limited to 1985 to 1999 for the surgical mortality comparison and calculations.

### RESULTS

#### Patients and Diagnoses

A total of 201 patients, 1.9% of the total NICU population for our time period, met the study criteria. The cardiac diagnoses of the patients in the study can be compared with data from 2 large incidence studies, the New England Regional Infant Cardiac Program\(^{10} \) and the Baltimore-Washington Infant Study.\(^{11-13} \) A few significant differences are seen. First, our incidence of VSD was similar to that found in the BWIS (study dates 1981 to 1989), both being higher than in the NERICP (study dates 1969 to 1974). Also of note is the increased incidence in our population of conotruncal defects, specifically truncus arteriosus and double outlet right ventricle, when compared with either the BWIS or the NERICP. The BWIS study included a table of diagnosis grouped by developmental mechanism as per Clark.\(^{14} \) When our data are grouped in this way and compared, all conotruncal defects are more prevalent in our population than in the BWIS group, whereas the other groups are similar. Septal defects and hemodynamic right-sided defects were less common in our patients.

#### Demographics

The male/female ratio was 1.09 (105 vs 96). The median gestational age was 33 weeks compared with 32 weeks for the comparison preterm group without CHD. The mean birth weight was 1852 g, whereas the mean birth weight for the comparison preterm group was 1533 g. Thus our population was slightly older and slightly larger than the general NICU population.
Fig 1 shows the CHD population plotted weight versus gestational age. The normal values are adapted from Zhang and Bowes'15 1995 series of 3,427,009 liveborn infants. The closed triangles represent the study group. The open triangles show 61 larger infants not included in the study group. They were excluded because we wished to limit the study group to only those infants at highest risk, that is, who were both low birth weight and premature. Larger infants listed as 34 to 36 weeks represent a group of near-term infants whose risks may not have differed significantly from those of term infants. Even when these larger infants are included for comparison, it is notable that most of the infants (62%) were below the 50th percentile, and a substantial number (23%) were below the 10th percentile.

Congenital Anomalies

Two thirds (n = 136, 68%) of the patients had no associated congenital anomaly apart from their CHD. The associated congenital syndromes found in the 32% of our patients who did have extracardiac malformations are shown in the Table. Of note, the lethal trisomies (13 and 18) were few in number (1% and 3%, respectively). Trisomy 21 also was infrequent in our preterm population. The other group primarily consisted of multiple congenital anomaly complexes, single noncardiac malformations, and 5 cases of DiGeorge syndrome, diagnosed on clinical evaluation. The incidence of the CATCH 22 deletion may be considerably higher than this, but fluorescent in situ hybridization was not available until the later years of the study period.

Morbidity

A comparison is made to the incidence of NEC and IVH in the entire NICU population in the same period. Results are shown in Fig 2. The incidence of severe (grade III-IV) IVH was significantly different in the 2 groups, with a lower incidence in the CHD group compared with the non-CHD NICU population. NEC, however, was significantly more common in our patients (9.5%) compared with the non-CHD group (5.7%). Six (32%) of the 19 preterm patients with NEC had at least one level of left-sided outflow obstruction; 4 (21%) had D-transposition of the great arteries. The overall incidence of these 2 types of lesions in our study group was 15% and 10%, respectively. Mortality attributable to NEC was high (5 of 19, 26%). Four patients, 2 of whom died after surgery, required bowel resection. Only 2 patients had undergone surgery for their CHD before NEC developed. One case occurred 17 days after Blalock-Hanlon atrial septectomy was performed for D-transposition of the great arteries/multiple VSDs, and the other occurred 50 days after interrupted aortic arch repair was performed. Neither patient required bowel resection, and both recovered.

Nonsurgical Group

No surgery was performed on 94 of the patients in the study at any time during the study period. This was for 3 general reasons. No surgery was required for the specific lesion in 51 patients (eg, small muscular VSD [n = 37]); pulmonary stenosis amenable to balloon valvuloplasty [n = 4]). Thirty patients had conditions that were deemed nonoperable by the team caring for the patient because of either medical instability or multiple severe anomalies including all of the lethal trisomy (13 and 18) patients. Ten patients died before an anticipated corrective or palliative procedure could be performed.

Surgical Group

A total of 108 patients underwent 133 cardiac surgical procedures. Sixty-three were closed heart operations, and 70 were open heart operations. Open heart procedures included VSD repair, arterial switch, Senning repair of transposition of the great arteries, truncus repair, repair of total anomalous pulmonary venous connection, and others. Four cardiac transplantations and 2 Norwood (stage 1) procedures, each for hypoplastic left heart syndrome, are included in this group. Closed heart procedures included pulmonary artery banding, coarctation repair, Blalock-Hanlon septectomy, and Blalock-Taussig shunt; 21 patients had a closed procedure followed later (not usually within the initial hospitalization) by an open procedure. These included
pulmonary artery banding with or without coarctation repair followed by VSD repair (n = 7) or repair of double outlet right ventricle (n = 2); Blalock-Taussig shunt followed by Fontan (n = 4) or tetralogy of Fallot repair (n = 4).

Mortality

The in-hospital mortality rate in our CHD group was significantly higher than that in the NICU population as a whole (26% vs 10%, P < .0001). The mean birth weight for survivors was 1737 g (range 558 to 2495 g) compared with that of 1712 g for nonsurvivors (range 780 to 2460 g), P = not significant. The median gestational age for both survivors and nonsurvivors was 33 weeks. For patients with congenital anomalies in addition to CHD, the in-hospital mortality rate was 39% (25 of 64); another 7 patients died at home or in a local hospital soon after transfer for a total mortality in these patients of 50%. Seven (78%) of 9 patients with hypoplastic left heart syndrome died; both survivors underwent heart transplantation. Other patients with single ventricle physiology also did poorly, with an overall mortality rate of 15 (68%) of 19. As did the NERICP, we found that the overall survival rate increased as the study period progressed, ranging from 44% in the period from 1976 to 1981 to 22% in the period from 1994 to 1999.

The overall surgical mortality rate from 1985 to the present, defined as death within 30 days of operation, is shown in Fig 3. The control group included infants <1 year of age who underwent cardiac surgery, minus our study group. Ten patients in the study group underwent both open and closed operation, not all in the initial hospitalization, were included for both procedures. The mortality rate for the closed procedure was 10.4% in the study group compared with 5.4% in the control group (difference not significant). The mortality rate for open procedures was higher, 25.4%, in the study group compared with 10.5% for the control group (P < .001). The mean birth weight was lower for nonsurvivors of both open and closed operations, but the differences were not statistically significant (1791 g vs 1952 g for open procedures; 1580 g vs 1709 g for closed). Dividing all patients into birth weight groups <2000 g and >2000 g for both types of procedure did not yield a significant difference in the mortality rate by χ² analysis.

Follow-up

Long-term follow-up was obtained on 134 of the 148 patients who survived to hospital discharge (mean age 5.6 years). Of the 134, 111 are still living, for an overall survival rate from birth of 55%. Most of the deaths that occurred in this group were within the first year of life. Nine of these patients had lethal trisomies or were deemed unable to undergo surgery, and they died early after discharge, as discussed previously. These patients are responsible for the steep early decline in the curve for the nonsurgical group. The other deaths in the nonsurgical group in the first year of life were of pneumonia (1), peritonitis (1), prolonged seizure (1), and unknown (2). Four patients aged 1 year or less died at cardiac operation, procedures including VSD closure (2), Senning atrial switch (1), or atrial septectomy (1) for transposition of the great arteries. One patient in the surgical group died of unknown causes, remote from operation.

Fig 4 shows the long-term survival curves. The actuarial survival rate at 10 years for all patients was 47%; exclusion of patients with small VSDs lowered this figure to 37%. Deaths were infrequent after the first 12 months. All late deaths were in the surgical group. Two were after Fontan completions at age 3 and 16 years in patients with tricuspid atresia (birth weights 1270 and 1956 g). The third occurred after fatal stroke and pulmonary embolus at age 9 years in a patient with severe Ebstein’s anomaly, occurring 2 months after tricuspid valve replacement (birth weight 2200 g). The fourth occurred suddenly at home; it was presumed to be caused by arrhythmia in a 14-year-old patient with un repaired D-transposition of the great arteries and severe pulmonary hypertension (s/p coarctation repair and Blalock-Hanlon septectomy in infancy).

Discussion

We have shown an increased prevalence of small for gestational age birth
in infants with CHD in a population of exclusively preterm infants. Previous studies also suggest a tendency for low birth weight in infants with CHD, although inconsistent correction for prematurity often confounds this finding. The Baltimore-Washington Infant study\(^{11}\) demonstrated a lower birth weight distribution for CHD cases versus a control group. The mean gestational age was not significantly different for cases and the control group, but the incidence of prematurity (defined as <37 weeks’ gestation) was higher: 13% versus 6%. Kramer et al\(^{17}\) found a group of 843 German newborns with CHD to have significantly lower birth weights than the general population. The prevalence of prematurity in their CHD population, however, was not increased. The NERICP\(^{16}\) found an overall lower distribution of birth weights in these infants with CHD compared with a normal control group, even when factors known to cause low birth weight such as chromosomal anomalies and congenital infection were excluded.

Our study sought to examine prematurity as a risk factor for poor outcome in CHD. We therefore excluded term but SGA infants and some larger infants reported to be in the 34- to 36-week range. Given the increased incidence of SGA birth in patients with CHD, this strict criterion is important to limit the study group to the premature infants who were at the highest risk. We are confident that few patients eligible for the study were missed by our data collection system. However, any preterm infant with a congenital heart lesion who received a diagnosis after discharge from the NICU was excluded from our study group by definition. Given the prolonged length of stay for most preterm infants compared with that of the term infants, few ductal dependent lesions such as hypoplastic left heart syndrome or critical coarctation that might be missed in a term nursery will be missed. Some milder lesions such as small to moderate VSD or mild pulmonary stenosis possibly were missed.

An estimate of the prevalence of CHD in the preterm population of middle Tennessee from our data would be invalid, given Vanderbilt’s status as a regional referral center for CHD. However, our data should be valid in estimating the frequency of extracardiac malformations and chromosomal abnormalities in preterm patients with CHD; our prevalence of isolated CHD of 68% is similar to studies of infants with CHD that do not separate term from preterm infants. Kramer et al\(^{17}\) reported 54.4% of German infants with CHD were isolated;\(^{17}\) the BWIS data found 73%\(^{18}\) NERICP 72%\(^{8}\) and Chang et al\(^{8}\) 70%. Thus our data show no increased incidence of associated extracardiac congenital anomalies in infants with CHD born prematurely.

With respect to conotruncal anomalies, our data and others’ suggest a tendency for premature birth in infants with these lesions. A recent European collaborative study described clinical features of 558 patients with DiGeorge syndrome, diagnosed by deletions within the DiGeorge critical region of chromosome 22.\(^{19}\) Significant cardiac defects were present in 409 (75%) of 545 patients for whom cardiac diagnoses were available; interrupted aortic arch comprised 14% and truncus arteriosus 9% of these diagnoses. Birth weight and gestational age data were available for 205 patients. A high proportion, 15%, were born before 37 weeks’ gestation. Most (84%) were in the normal range of birth weight for gestational age. We are unable to report data on chromosomal evidence of DiGeorge in our preterm CHD population, but this would be a plausible explanation for our high incidence of conotruncal anomalies. An alternate explanation for our finding would be a higher incidence in the general population of our referral area of conotruncal anomalies.

Our morbidity and mortality data confirm what most clinicians would expect: preterm infants with CHD do less well than preterm infants without CHD. The increased incidence of NEC in particular is compelling. Previous studies have estimated the incidence of NEC in term infants with CHD to be as high as 7%\(^{20}\) whereas the incidence in NICU admissions is...
reported to be between 1% and 5%.21 Thus our data show a compounding effect of prematurity with CHD on risk for NEC. The overall mortality rate for infants in an NICU with NEC has been found to be between 20% and 40%.17 Our mortality rate was in the middle of this range. Severe IVH, on the other hand, appears to be more a function of younger gestational age or small size, because it was significantly less frequent in the patients with CHD.

Preterm infants with CHD also do less well at cardiac surgery than term infants. Several recent studies have examined surgical outcomes in infants undergoing cardiac operation at weights <2500 g with encouraging results. Rossi et al8 reported a series of 30 infants weighing 2000 g or less with a hospital survival rate of 83% and an overall survival rate at 13 months of 67%;24 of the infants were premature, with the remaining SGA, mostly twin gestation, term infants. All in-hospital deaths (n = 5) were in premature infants. Reddy et al9 looked at 102 such patients with a median weight of 2100 g, 66 of whom were premature (<37 weeks’ gestation). The early mortality rate was 10%, and the actuarial survival rate at 1 year was 82%. Also important, freedom from reinter- vention at 1 year was 91%. Regression analysis revealed no association between weight or gestational age with survival; factors that did correlate were longer bypass time, complex anomalies, and diagnosis of truncus arteriosus. The authors comment that delayed intervention, for example, a period of medical management to allow growth, was associated with increased preoperative morbidity.

Others have addressed the question of delayed medical management before surgical intervention for CHD in very small infants. Chang et al6 reported a 70% hospital survival rate in 100 infants with birth weights ≤2500 g (77 premature infants) with congenital heart lesions. Patients were divided into early intervention (initial hospitalization), late intervention (after initial hospitalization, mean age 4.5 months), and no intervention (lethal or grave prognosis). This study included a subgroup of very low birth weight infants (≤1500 g, n = 18), evenly distributed among the 3 intervention categories, with a survival rate of only 50%. Presumably this group included only preterm infants; however, the data are not presented with regard to gestational age. It is not clear whether prematurity affected the decision for the type of intervention or overall survival. Still, the mortality rate in the early intervention group was 19%, compared with 31% in the late intervention group. The authors thus advocate early surgical intervention, because many of the deaths in the late intervention group occurred during medical management rather than as operative deaths. The early (hospital) mortality rate was 16.5% in 60 infants weighing <2.5 kg who underwent cardiopulmonary bypass.7 The mean weight was 2.1 kg, and 25% were <34 weeks’ gestation at operation. Within their study group, age and weight did not emerge as significant risk factors; however, a comparison group of infants larger than 2.5 kg but <6 months of age had a significantly lower mortality rate. The authors conclude that surgery in small infants with CHD in need of urgent repair should not be delayed in anticipation of a better result with weight gain. We also were unable to find a statistically significant difference in gestational age or birth weight between survivors and infants who died, overall or after surgery.

Kirklin et al2 looked at infants <3 months of age who underwent cardiac surgery in the period 1967 to 1980. The authors do not comment on the number of premature infants included in the study group. The mortality rate was 43% for open operations (n = 170) compared with 22% for closed operations (n = 161). Taken together, our data and the studies discussed previously reveal an encouraging trend toward better surgical outcomes in small and preterm infants with CHD and less justification for a prolonged waiting period before surgery in these patients. Still, these patients remain a medical and surgical challenge for a multidisciplinary team of caregivers.

REFERENCES


FELLOWSHIPS

Fellowships available in pediatric subspecialities and those for general academic pediatric training are listed once a year, in January, in The Journal of Pediatrics. Each June, forms for listing fellowships available for the academic year beginning 18 months after publication are sent to the Chairman of the Department of Pediatrics at major hospitals in the United States and Canada. In addition, a copy of the application form appears in the July, August, and September issues of The Journal (please use the current form). Should you desire to list fellowships, a separate application must be made each year for each position. All applications must be returned to Mosby, Inc, by October 15 preceding the listing year to ensure publication. Additional forms will be supplied on request from the Periodical Editing Department, Mosby, Inc, 11830 Westline Industrial Dr, St Louis, MO 63146-3318 (phone: 800-325-4177, ext 2838, or 314-579-2838).