

# The New England Journal of Medicine

©Copyright, 1995, by the Massachusetts Medical Society

Volume 332

MARCH 2, 1995

Number 9

## DEVELOPMENTAL AND NEUROLOGIC STATUS OF CHILDREN AFTER HEART SURGERY WITH HYPOTHERMIC CIRCULATORY ARREST OR LOW-FLOW CARDIOPULMONARY BYPASS

DAVID C. BELLINGER, PH.D., RICHARD A. JONAS, M.D., LEONARD A. RAPPAPORT, M.D., DAVID WYPIJ, PH.D., GIL WERNOVSKY, M.D., KARL C.K. KUBAN, M.D., PATRICK D. BARNES, M.D., GREGORY L. HOLMES, M.D., PAUL R. HICKEY, M.D., ROY D. STRAND, M.D., AMY Z. WALSH, R.N., B.S.N., SANDRA L. HELMERS, M.D., JULES E. CONSTANTINOU, F.R.A.C.P., ENRIQUE J. CARRAZANA, M.D., JOHN E. MAYER, M.D., FRANK L. HANLEY, M.D., ALDO R. CASTANEDA, M.D., JAMES H. WARE, PH.D., AND JANE W. NEWBURGER, M.D., M.P.H.

**Abstract Background.** Deep hypothermia with either total circulatory arrest or low-flow cardiopulmonary bypass is used to support vital organs during heart surgery in infants. We compared the developmental and neurologic sequelae of these two strategies one year after surgery.

**Methods.** Infants with D-transposition of the great arteries who underwent an arterial-switch operation were randomly assigned to a method of support consisting predominantly of circulatory arrest or a method consisting predominantly of low-flow bypass. Developmental and neurologic evaluations and magnetic resonance imaging (MRI) were performed at one year of age.

**Results.** Of the 171 patients enrolled in the study, 155 were evaluated. After adjustment for the presence or absence of a ventricular septal defect, the infants assigned to circulatory arrest, as compared with those assigned to low-flow bypass, had a lower mean score on the Psychomotor Development Index of the Bayley Scales of Infant Development (a 6.5-point deficit,  $P=0.01$ ) and a higher

proportion had scores  $\leq 80$  (i.e., 2 SD or more below the population mean) (27 percent vs. 12 percent,  $P=0.02$ ). The score on the Psychomotor Development Index was inversely related to the duration of circulatory arrest ( $P=0.02$ ). The risk of neurologic abnormalities increased with the duration of circulatory arrest ( $P=0.04$ ). The method of support was not associated with the prevalence of abnormalities on MRI scans of the brain, scores on the Mental Development Index of the Bayley Scale, or scores on a test of visual-recognition memory. Perioperative electroencephalographic seizure activity was associated with lower scores on the Psychomotor Development Index ( $P=0.002$ ) and an increased likelihood of abnormalities on MRI scans of the brain ( $P<0.001$ ).

**Conclusions.** Heart surgery performed with circulatory arrest as the predominant support strategy is associated with a higher risk of delayed motor development and neurologic abnormalities at the age of one year than is surgery with low-flow bypass as the predominant support strategy. (N Engl J Med 1995;332:549-55.)

DEEP hypothermia with total circulatory arrest is a method of support for vital organs that is often used during the repair of complex congenital heart abnormalities in infants. The maximal duration of circulatory arrest that will not result in impairment of the central nervous system is uncertain.<sup>1,2</sup> Few data are available on the developmental and neurologic sequelae of the most important alternative support strategy, continuous low-flow cardiopulmonary bypass.<sup>3</sup>

In 1988 we began a randomized clinical trial to com-

pare the incidence of brain injury in children with D-transposition of the great arteries undergoing an arterial-switch operation after assignment to a strategy consisting predominantly of circulatory arrest with that in children assigned to a strategy consisting predominantly of low-flow cardiopulmonary bypass. In the early postoperative period, the infants assigned to circulatory arrest had a higher incidence of neurologic morbidity than those assigned to low-flow bypass, including a higher incidence of seizures and ictal activity on continuous electroencephalographic (EEG) monitoring, a longer time to the reappearance of normal brain EEG activities, and release of greater amounts of the brain isoenzyme of creatine kinase.<sup>4</sup> In this report we compare the developmental and neurologic status of the children in the two groups at one year.

### METHODS

Between April 1988 and February 1992, we enrolled 171 patients in a prospective, randomized, single-center trial. The eligibility criteria included a diagnosis of D-transposition of the great arteries with

From the Departments of Neurology (D.C.B., K.C.K.K., G.L.H., S.L.H., J.E.C., E.J.C.), Cardiovascular Surgery (R.A.J., J.E.M., F.L.H., A.R.C.), Medicine (L.A.R.), Cardiology (G.W., A.Z.W., J.W.N.), Anesthesia (P.R.H.), and Radiology (P.D.B., R.D.S.), Children's Hospital; the Departments of Neurology (D.C.B., K.C.K.K., G.L.H., S.L.H., J.E.C., E.J.C.), Surgery (R.A.J., J.E.M., F.L.H., A.R.C.), Pediatrics (L.A.R., G.W., J.W.N.), and Radiology (P.D.B., R.D.S.), Harvard Medical School; and the Department of Biostatistics, Harvard School of Public Health (D.W., J.H.W.) — all in Boston. Address reprint requests to Dr. Newburger at the Department of Cardiology, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.

Supported by grants (HL41786, RR02172, and P30-HD18655) from the National Institutes of Health.

either an intact ventricular septum or a ventricular septal defect, a scheduled repair to be performed by three months of age, and coronary-artery anatomy considered suitable for the arterial-switch operation. Exclusion criteria included a birth weight below 2.5 kg, a recognizable syndrome of congenital anomalies, associated extracardiac anomalies that were moderate or severe, previous cardiac surgery, or associated cardiovascular anomalies requiring reconstruction of the aortic arch or additional open surgical procedures. Informed consent was obtained from the parents of all the infants. Additional information about the study design, perfusion methods, surgical techniques, and anesthetic management was presented previously.<sup>4</sup>

Information on family characteristics<sup>5,6</sup> was obtained from interviews with the parents. Prenatal and perinatal data were also recorded. Examination of the children at the age of one year was performed by investigators who were unaware of the treatment assignment or clinical course.

### Developmental Testing

All assessments were conducted at 8 a.m. Two examiners administered the Bayley Scales of Infant Development,<sup>7</sup> which yield scores on two indexes: the Psychomotor Development Index and the Mental Development Index. We also calculated the proportion of children whose scores were less than or equal to 80 (approximately 2 SD below the current mean scores on the 1969 version of this test<sup>8</sup>). An evaluation of interexaminer reliability (13 infants) showed that the examiners were in agreement for 99 percent of the individual items, and correlations between the raw scores were higher than 0.99.

The Fagan Test of Infant Intelligence,<sup>9</sup> which assesses visual-recognition memory, was also administered. The mean novelty-preference score (percentage of time spent looking at a novel stimulus) was computed, and children with scores lower than 53 percent were considered to have failed the test.<sup>9</sup>

### Neurologic Examination

Neurologic examinations were performed by a pediatric neurologist using the format derived from the National Collaborative Perinatal Project. Findings were classified as normal, possibly abnormal, or definitely abnormal. Abnormalities were subclassified according to type (cerebral palsy, tone alteration, ataxia or dysmetria, focal abnormalities, and abnormalities of the special senses).<sup>10-13</sup> Children who had cerebral palsy were excluded from classification in other categories.

### Magnetic Resonance Imaging

Patients underwent magnetic resonance imaging (MRI) of the brain with a 1.5-tesla system (General Electric Medical, Milwaukee). We used conventional spin-echo techniques, including sagittal T<sub>1</sub>-weighted images (repetition time, 600 msec; echo time, 15 msec; number of signals averaged [NSA], 2) and axial proton-density-weighted and T<sub>2</sub>-weighted images (repetition time, 2000 msec; echo time, 90 msec; NSA, 2). A slice thickness of 5 mm was used with 1.0 to 2.5 mm of spacing between slices and a 24-cm field of view. Gadolinium enhancement was not used.

Two pediatric neuroradiologists independently assessed structural and intensity abnormalities. The findings were classified as normal, possibly abnormal, or definitely abnormal (mild, moderate, or severe). Abnormalities were subclassified as diffuse (ventricular dilatation, delayed myelination or maturation, or periventricular leukomalacia), focal or multifocal (atrophy or intensity abnormality of gray or white matter), or developmental (incidental). In cases of conflicting assessments (14 percent of the studies, with 4 percent frank disagreement), the two examiners reached an agreement.

### Statistical Analysis

The two treatment groups were compared in intention-to-treat analyses. Secondary analyses examined the effect of the duration (in minutes) of total circulatory arrest on the outcome. All tests of hypotheses and regression analyses of outcome variables were adjusted for the diagnosis (i.e., intact ventricular septum or ventricular septal defect). Adjustment for the surgeon or for an interaction between the surgeon and the treatment did not alter the results.

The outcomes at one year included both continuous and categorical variables. Multiple linear-regression methods and Wilcoxon rank-sum tests were used to analyze continuous variables. Stratified exact

tests<sup>14</sup> and multiple logistic-regression methods were used to analyze categorical variables.

Scores on the Bayley Scales were expressed in two ways. First, the standard scores on the Psychomotor Development Index and the Mental Development Index were derived.<sup>7</sup> Second, for each scale, the numbers of items passed were totaled and adjusted for age at the time of examination by means of an analysis of covariance. This approach adjusts for imbalances between treatment and diagnostic groups in the assignment of children to the age intervals used to derive standard scores.

For some children, not all outcome scores were available. Analyses were based on scores on the Psychomotor Development Index for 142 children and on scores on the Mental Development Index for 143 children. One child was too distressed for the administration of any developmental tests. Testing of another child had to be terminated before completion of the Psychomotor Development Index. A third child, later found to be autistic, could not be tested because of reduced social relatedness. In addition, before data analysis and without knowledge of the treatment assignments, a decision was made to exclude the developmental scores of the first 10 children who returned for examinations at one year. We had enrolled these 10 children to demonstrate our ability to assign children randomly to treatment groups at the time of surgery. At one year, these infants were evaluated under conditions that were not standardized in terms of time, location, and the children's condition. The National Institutes of Health Data and Safety Monitoring Committee for the trial approved our decision not to include these children in analyses of developmental end points.

Analyses of the Fagan test are based on the scores of 107 children. Twenty children were excluded because they were not within the age range of 11 to 13 months at the time of examination. Seventeen children had incomplete tests because of their inability to cooperate. (The 10 children first enrolled and the autistic child were also not included.)

Neurologic examinations were completed for 154 children, and MRI examinations for 142. The most common reason for the unavailability of MRI scans was parental refusal to grant consent. The percentages of children for whom data were not available for the different end points did not differ significantly according to whether they underwent surgery with circulatory arrest or low-flow bypass.

## RESULTS

Of the 171 infants enrolled in the trial, 168 were alive at one year of age, and 155 (92 percent) returned for evaluation. Seventy-six percent were boys, and 89 percent were white. Of the 13 infants who did not return for the one-year evaluation (7 assigned to circulatory arrest and 6 to low-flow bypass), 9 did not return because their parents decided not to participate, 2 could not be located, and 2 were living in other countries. The children who returned for evaluation did not differ significantly from those who did not with respect to sociodemographic factors, intraoperative perfusion variables, or preoperative and postoperative neurologic status. However, the children who did not return had a longer median period of intubation (3.4 vs. 2.9 days,  $P=0.02$  by the Wilcoxon test) and a longer median hospital stay (11 vs. 9 days,  $P=0.08$  by the Wilcoxon test).

Of the children who returned for evaluation, 120 (77 percent) had an intact ventricular septum, and 35 (23 percent) had a ventricular septal defect (Table 1). Treatment groups for each diagnosis were similar with respect to preoperative variables, sociodemographic variables, and interim medical history. However, the infants with a diagnosis of ventricular septal defect were older at the time of surgery, making it difficult to distinguish the independent contributions of age at the time of surgery and diagnosis to the status at one year.

**Table 1. Characteristics of Infants with D-Transposition of the Great Arteries, According to Ventricular Septal Status and Treatment Group.\***

VARIABLE	INTACT VENTRICULAR SEPTUM		VENTRICULAR SEPTAL DEFECT	
	CIRCULATORY ARREST (N = 61)	LOW-FLOW BYPASS (N = 59)	CIRCULATORY ARREST (N = 18)	LOW-FLOW BYPASS (N = 17)
	<i>mean ±SD</i>			
<b>Preoperative characteristics</b>				
Birth weight (g)	3601±470	3480±414	3436±270	3564±344
Gestational age (wk)	39.8±1.3	39.7±1.1	40.1±1.2	39.4±1.0
Apgar score at 5 min	8.1±1.0	8.4±0.7	8.7±0.5	8.6±0.6
Age at surgery (days)	7.6±5.7	7.0±3.9	24.1±21.4	13.8±17.5
<b>Surgical data</b>				
Circulatory arrest (min)	52±13	14±12	54±8	33±16
Total bypass time (min)	81±28	127±26	114±26	124±16
Total support time (min)	134±31	141±31	168±27	157±20
	<i>no. with abnormality/total no. (%)</i>			
<b>Postoperative neurologic abnormalities</b>				
Clinical seizures within 7 days	3/61 (5)	0/59	5/18 (28)	1/17 (6)
Ictal activity within 48 hr†	7/54 (13)	6/46 (13)	10/15 (67)	2/11 (18)
	<i>mean ±SD</i>			
<b>Follow-up data at 1 year</b>				
Age (mo)	12.4±0.8	12.5±0.8	12.1±0.4	12.4±0.9
Weight (z score)	-0.30±1.04	-0.41±0.87	-0.62±0.94	-0.18±0.77
Length (z score)	0.17±1.68	-0.37±1.90	-1.11±2.17	-0.74±1.15
Social class‡	41±15	45±14	43±13	40±15
Maternal IQ§	95±14	98±13	95±8	98±14

\*Only the 155 children who returned for evaluation at one year of age are included.  
 †Rhythmic epileptiform activity continuing for more than five seconds on continuous video EEG monitoring.  
 ‡Score on the Hollingshead Four Factor Index of Social Status, with higher scores indicating higher social status.<sup>5</sup>  
 §Score on the Peabody Picture Vocabulary Test (revised).<sup>6</sup>

The treatment groups did not differ in terms of age-adjusted weight or length at one year.

During the period between the neonatal arterial-switch operation and the one-year evaluation, 78 children (51 percent of those for whom data were available) underwent cardiac catheterization, and 1 child (who had an intact ventricular septum and was assigned to low-flow bypass) underwent additional cardiac surgery. At the time of the one-year evaluation, 11 children (7 percent) were receiving digoxin, and 2 (1 percent) were receiving diuretics. No child had nonfebrile seizures after hospital discharge. Two children (1 percent) had febrile seizures; neither had seizures detected clinically or by EEG monitoring in the perioperative period.

**Developmental Testing**

*Psychomotor Development Index*

The mean (±SD) score on the Psychomotor Development Index for the two treatment groups combined was 95.1±15.5. Scores were significantly lower among the children assigned to circulatory arrest (mean difference between the two groups, 6.5 points; 95 percent confidence interval, 1.6 to 11.5; P=0.01) (Table 2). Lower scores were also associated with a longer duration of circulatory arrest (P=0.02) (Fig. 1). None of various nonlinear or piecewise linear models of this association fit the data significantly better than did a linear model. With adjustment for age at the time of examination, the number of scale items passed was lower for children assigned to circulatory arrest (P=0.003) and was in-

versely related to the duration of circulatory arrest (P=0.008). Twenty percent of the children (28 of 142) had a score less than or equal to 80. Lower scores were more prevalent among the children assigned to circulatory arrest (27 percent vs. 12 percent; exact P=0.02) and those with a longer duration of circulatory arrest (P=0.03).

The effect of the treatment assignment on scores on the Psychomotor Development Index could not be explained by any of the perioperative or sociodemographic variables measured. In multiple-regression models, scores were positively related to birth weight, but adjustment for this variable did not appreciably alter the treatment-group effect. A diagnosis of ventricular septal defect was an independent risk factor for a lower score (mean difference between the two groups, 6.6 points; 95 percent confidence interval, 0.7 to 12.6; P=0.03).

*Mental Development Index*

The score on the Mental Development Index for the two treatment groups combined was 105.1±15.0.

Scores tended to be lower among children assigned to circulatory arrest (mean difference, 4.1 points; 95 percent confidence interval, -0.7 to 8.8; P=0.10) (Table 2), although the scores did not decrease significantly with an increased duration of circulatory arrest (P=0.33). With adjustment for age at the time of examination, the number of scale items passed was lower among children assigned to circulatory arrest (P=0.04) but was not significantly related to the duration of circulatory arrest (P=0.16). Of the eight children with scores less than or equal to 80, six were assigned to circulatory arrest (exact P=0.27). In multiple-regression models, lower scores on the Mental Development Index were significantly associated with a lower level of maternal education, but adjustment for this variable did not appreciably alter the treatment-group effect. A diagnosis of ventricular septal defect was an independent risk factor for a lower score (mean difference, 8.6 points; 95 percent confidence interval, 2.8 to 14.4; P=0.004).

*Fagan Test of Infant Intelligence*

The mean novelty-preference score for the two groups combined was 58.8±7.6 percent. Scores were not related to the treatment assignment (Table 2) or the duration of circulatory arrest. A diagnosis of ventricular septal defect was associated with lower scores (mean difference, 3.6 percent; 95 percent confidence interval, 0.2 to 7.0; P=0.04).

Although 21 percent of the children (23 of 107) had test scores indicating failure (i.e., less than 53 percent),

the percentage of such scores did not differ significantly according to the treatment group (circulatory arrest, 25 percent; low-flow bypass, 17 percent) or diagnosis (intact ventricular septum, 19 percent; ventricular septal defect, 29 percent). Inability to complete the test was not associated with the treatment assignment.

### Neurologic Examination

Five of the 154 children who underwent neurologic examination (3 percent) had possible abnormalities, and 48 (31 percent) had definite abnormalities, all of which were judged to be mild. Neurologic abnormalities tended to be more common among the children assigned to circulatory arrest than among those assigned to low-flow bypass (41 percent vs. 28 percent; exact  $P=0.09$ ) (Table 3). Similarly, possible or definite neurologic abnormalities were associated with a longer duration of circulatory arrest ( $P=0.04$ ) (Fig. 2). A low Apgar score at five minutes and a young gestational age were both independent risk factors for neurologic abnormalities, but adjustment for these factors did not appreciably affect the estimate of the increased risk associated with assignment to circulatory arrest. A total of 28 children (18 percent) had hypotonia, 12 (8 percent) had hypertonia, 7 (5 percent) had cerebral palsy, 4 (3 percent) had focal abnormalities, and 2 (1 percent) had abnormalities of special senses. The occurrence of specific abnormalities was not associated with the treatment assignment or the duration of circulatory arrest.

### Magnetic Resonance Imaging

Eleven of the 142 children (8 percent) who underwent MRI had possible abnormalities, and 22 (15 percent) had definite abnormalities, which were judged to be mild in 86 percent of these children. The abnormalities were classified as focal or multifocal in 20 children, diffuse in 16, and developmental or incidental in 3 (i.e., left temporal lobar hypoplasia, Chiari type I malformation, or a small arachnoid cyst in the left sylvian fissure).

The prevalence of possible or definite abnormalities

Table 2. Scores on Developmental Tests, According to Ventricular Septal Status and Treatment Group.

TEST	INTACT VENTRICULAR SEPTUM		VENTRICULAR SEPTAL DEFECT		P VALUE*
	CIRCULATORY ARREST	LOW-FLOW BYPASS	CIRCULATORY ARREST	LOW-FLOW BYPASS	
	<i>mean ±SD</i>				
Psychomotor Development Index	94.1±15.3	99.1±14.2	84.2±18.7	96.0±11.1	0.01
Mental Development Index	106.0±15.6	108.0±12.4	92.8±15.7	104.3±15.1	0.10
Fagan Test of Infant Intelligence†	59.4±7.1	59.8±6.2	54.6±10.7	57.5±9.0	0.49
	<i>no. with low score/total no. (%)</i>				
Psychomotor Development Index ≤80	12/57 (21)	5/54 (9)	8/16 (50)	3/15 (20)	0.02
Mental Development Index ≤80	3/58 (5)	1/54 (2)	3/16 (19)	1/15 (7)	0.27
Fagan Test <53†	10/42 (24)	6/41 (15)	4/13 (31)	3/11 (27)	0.35

\*P values are for differences between treatment groups, with adjustment for diagnosis; P values were determined by linear regression for continuous outcome variables and by stratified exact tests for dichotomous outcome variables.

†Restricted to infants between 11 and 13 months of age at the time of examination.

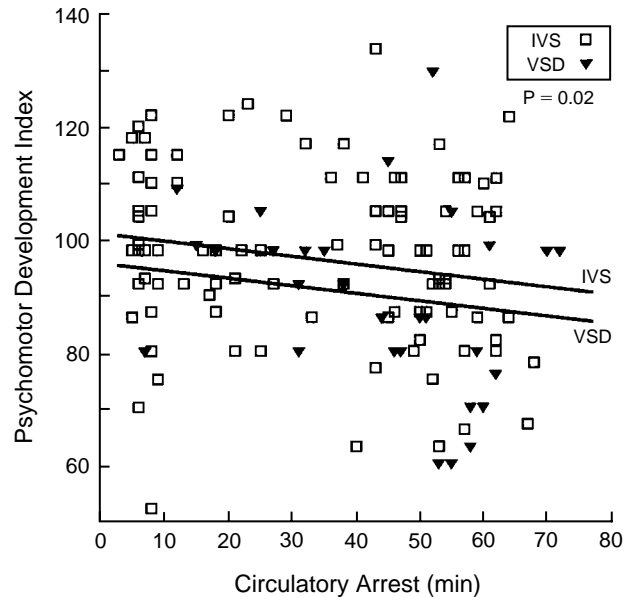


Figure 1. Score on the Psychomotor Development Index at One Year as a Function of the Duration of Total Circulatory Arrest.

Regression lines are shown for infants with an intact ventricular septum (IVS) and those with a ventricular septal defect (VSD). The P value shown was calculated by linear regression for the effect of the duration of total circulatory arrest on the score on the Psychomotor Development Index, with adjustment for diagnosis.

was not related to the treatment assignment, the duration of circulatory arrest, or an associated diagnosis of ventricular septal defect. Preoperative acidosis, however, was a significant risk factor for abnormalities detected on MRI scanning.

### Relation between Perioperative Seizure Activity and Status at One Year

During the first 48 hours after surgery, the infants assigned to circulatory arrest had a significantly higher risk of seizure activity, detected by continuous EEG monitoring, than the infants assigned to low-flow bypass.<sup>4</sup> In regression analyses with adjustment for the treatment group and the presence or absence of a ventricular septal defect, the occurrence of EEG seizure activity in the early postoperative period was associated with a mean reduction of 11.2 points on the Psychomotor Development Index ( $P=0.002$ ) and with a significantly higher risk of possible or definite abnormalities on MRI scanning (odds ratio, 9.4; 95 percent confidence interval, 2.7 to 32.3;  $P<0.001$ ). The children assigned to circulatory arrest also had an increased risk of clinical seizures in the early postoperative period.<sup>4</sup> Despite the limited statistical power of the analysis, the occurrence of clinical seizures was associated with an

Table 3. Neurologic Outcomes According to Ventricular Septal Status and Treatment Group.

VARIABLE	INTACT VENTRICULAR SEPTUM		VENTRICULAR SEPTAL DEFECT		P VALUE*
	CIRCULATORY ARREST (N=60)	LOW-FLOW BYPASS (N=59)	CIRCULATORY ARREST (N=18)	LOW-FLOW BYPASS (N=17)	
	<i>no. with abnormality (%)</i>				
Overall abnormalities					0.09†
Possible	2 (3)	1 (2)	2 (11)	0	
Definite‡	21 (35)	13 (22)	7 (39)	7 (41)	
Specific abnormalities					0.72
Cerebral palsy	3 (5)	3 (5)	0	1 (6)	
Tone alteration§					
Hypotonia	11 (18)	7 (12)	7 (39)	3 (18)	0.14
Hypertonia	5 (8)	3 (5)	0	4 (24)	0.56
Ataxia or dysmetria	1 (2)	0	0	0	1.00
Focal abnormalities§	1 (2)	1 (2)	1 (6)	1 (6)	1.00
Abnormalities of special senses	1 (2)	1 (2)	0	0	1.00

\*P values, determined with stratified exact tests, are for differences between treatment groups, with adjustment for diagnosis.

†For the comparison between normal results and possibly or definitely abnormal results.

‡All definite abnormalities were judged to be mild.

§In patients without cerebral palsy.

increased risk of possible or definite neurologic abnormalities at one year (P=0.05).

**DISCUSSION**

We found that a strategy of support consisting predominantly of circulatory arrest during open-heart surgery in infants, as compared with a strategy consisting predominantly of low-flow cardiopulmonary bypass, was associated with worse performance on tests of developmental and neurologic function at the age of one year. Moreover, longer duration of circulatory arrest was associated with increased risk of delayed psychomotor development and neurologic abnormalities at one year. The magnitude of the effect was modest, since the difference between the scores on the Psychomotor Development Index for the two treatment groups was approximately 0.4 SD. However, trends toward a more favorable outcome for children assigned to low-flow bypass were evident for many of the end points measured. These findings are consistent with the higher risk of neurologic morbidity in the early postoperative period previously reported for the children randomly assigned to circulatory arrest.<sup>4</sup> In addition, seizure activity detected on continuous EEG monitoring during the early postoperative period and a diagnosis of ventricular septal defect were independent risk factors for a poor outcome.

The duration of circulatory arrest that is safe (the period during which no irreversible central nervous system damage occurs) is unknown. Studies in animals suggest that periods of arrest that are shorter than 30 minutes at brain temperatures of 15 to 20°C do not result in permanent structural or functional damage.<sup>1,15</sup> In follow-up studies of children who had undergone open-heart surgery,<sup>3,16-23</sup> developmental impairment was associated with periods of arrest that were longer than 60 minutes (at brain temperatures of 18 to 20°C) and possibly with periods as short as 45 minutes. Modifying factors may include the depth of hypothermia, the na-

ture of the cooling process, cerebral blood flow during cooling and re-warming, and blood pH values and arterial carbon dioxide tension during cooling.<sup>3,24</sup>

Although we were unable to determine a threshold for the duration of circulatory arrest below which no increase in risk was evident, the data are consistent with the hypothesis that a period shorter than 35 minutes (at 18°C) has a minimal adverse effect on scores on the Psychomotor Development Index at one year. Substantial deficits seemed to be most prevalent among the children with circulatory-arrest periods longer than 45 minutes. Our ability to establish a threshold was limited by the modest effect of the duration of circulatory arrest and the considerable degree of scatter in the data.

Although this study was designed to compare treatment strategies and did not include a normal control group, the scores of patients in both treatment groups were considerably below average. The mean novelty-preference score was similar to that for other infants at risk for impaired cognitive development.<sup>9</sup> The mean scores on the Bayley Scales were approximately 0.5 SD

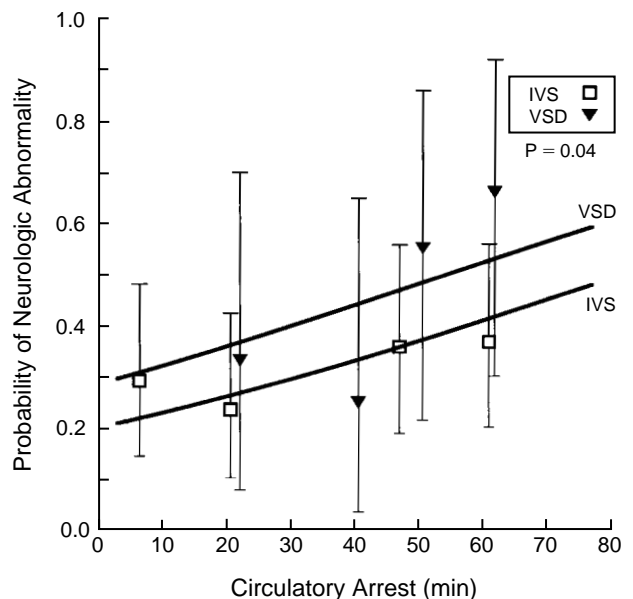


Figure 2. Estimated Probability of a Possible or Definite Neurologic Abnormality at One Year as a Function of the Duration of Total Circulatory Arrest.

Logistic-regression lines are shown for children with an intact ventricular septum (IVS) and those with a ventricular septal defect (VSD). Point estimates and exact 95 percent confidence intervals for outcome probabilities are plotted for the means of each quartile for the duration of circulatory arrest. The P value was calculated by logistic regression for the effect of the duration of circulatory arrest on the neurologic outcome, with adjustment for diagnosis.

(for the Mental Development Index) to 1 SD (for the Psychomotor Development Index) lower than population norms.<sup>25</sup> Apart from the duration of circulatory arrest, these low scores may be associated with preoperative cyanosis or hemodynamic instability, the generally deleterious effects of cardiopulmonary bypass on the central nervous system (e.g., microembolism and hypoperfusion), or the adverse effects of hemodynamic conditions in the postoperative period.

Nearly one quarter of the patients had possible or definite abnormalities on MRI scans, a finding that is relatively common after open-heart surgery in children and adults.<sup>26,27</sup> These abnormalities included both diffuse global or watershed (border-zone) injuries related to hypoperfusion or to hypoxia or ischemia and focal or multifocal lesions presumed to be macroembolic. Periventricular leukomalacia, selective neuronal necrosis, focal or multifocal ischemic brain necrosis, and parasagittal cerebral lesions have been reported in infants with congenital heart disease.<sup>28-31</sup> White-matter injury, reported in infants after cardiac surgery,<sup>28,29</sup> could account for the observed motor deficits. The topography of both neuronal and white-matter injury after heart surgery in infants is consistent with ischemia as an important pathogenetic factor.<sup>32</sup>

EEG evidence of seizures during the first 48 hours after surgery was common in the study cohort, and infants with seizures had worse outcomes at one year of age than infants without postoperative seizures. Indeed, ictal activity on EEG monitoring in the first 48 hours after surgery was one of the strongest predictors of outcome, which is consistent with the findings in studies of neonates with other conditions.<sup>33</sup> At a developmental stage similar to that of the human infant at birth, the infant rat brain is highly vulnerable to post-ischemic seizures; this epileptic activity is correlated with the degree of neuronal injury and neurologic sequelae.<sup>34-36</sup> It is not clear whether the occurrence of seizures reflects an underlying brain injury or contributes independently to the injury.<sup>37</sup>

Several limitations inherent in the use of infant developmental testing at one year of age warrant comment. Although tests such as the Bayley Scales have satisfactory concurrent validity, the scores of one-year-old children have limited predictive validity.<sup>38,39</sup> The relative deficits of the children assigned to circulatory arrest were most prominent in the domain of motor function, but assessments at older ages may reveal treatment effects in other domains, such as language or visual-motor integration, that are not easily tested in very young children.<sup>40</sup>

In summary, at one year of age the developmental and neurologic status of children randomly assigned to a strategy consisting predominantly of total circulatory arrest as a method of supporting vital organs during heart surgery was worse than that of children randomly assigned to a strategy consisting predominantly of low-flow bypass. Assessments of the children as they approach school age will clarify whether these findings portend clinically important differences in academic functioning. In treating individual infants, cardiovascu-

lar surgeons must balance the technical advantages of total circulatory arrest with its potential disadvantages.

We are indebted to the members of the Safety and Data Monitoring Committee — Julien I.E. Hoffman, M.D. (chairman), John W. Kirklin, M.D., Barry M. Lester, Ph.D., Robert J. Levine, M.D., Eli M. Mizrahi, M.D., Joseph G. Reves, M.D., George W. Williams, Ph.D., and Joel I. Verter, Ph.D.; to the perfusionists — David M. Farrell, M.A., C.C.P., Willis G. Gieser, C.C.P., Robert A. LaPierre, B.S., C.C.P., Robert J. Howe, B.S., C.C.P., and Bettina Archilla, B.S.; to the electroencephalographers — Lewis Kull, Sheila A. McPeck, Susan M. Hegarty, and Wayne A. Cote; to Ludmila Kyn for data-base and statistical programming; to the nursing staff for assistance with adherence to the protocol; to Donna M. Donati, Donna M. Duva, and Lisa-Jean Buckley for data management; to Kathleen M. O'Brien for project coordination; and to Edward Z. Tronick, Ph.D., for the use of a testing suite in the Child Development Unit, Children's Hospital.

## REFERENCES

- Folkerth TL, Angell WW, Fosburg RG, Oury JH. Effect of deep hypothermia, limited cardiopulmonary bypass and total arrest on growing puppies. In: Roy P-E, Roma G, eds. The metabolism of contraction. Vol. 10 of Recent advances in studies on cardiac structure and metabolism. Baltimore: University Park Press, 1975:411-21.
- Molina JE, Einzig S, Mastro AR, et al. Brain damage in profound hypothermia: perfusion versus circulatory arrest. *J Thorac Cardiovasc Surg* 1984;87:596-604.
- Kirklin JW, Barratt-Boyes BG. Cardiac surgery: morphology, diagnostic criteria, natural history, techniques, results, and indications. Vol. 1. 2nd ed. New York: Churchill Livingstone, 1993.
- Newburger JW, Jonas RA, 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.
- Hollingshead A. Four factor index of social status. New Haven, Conn.: Department of Sociology, Yale University, 1975.
- Dunn L, Dunn L. The Peabody Picture Vocabulary Test: manual for forms L and M. Rev. ed. Circles Pines, Minn.: American Guidance Service, 1981.
- Bayley N. Manual for the Bayley Scales of Infant Development. New York: Psychological Corporation, 1969.
- Idem*. Manual for the Bayley Scales of Infant Development. 2nd ed. San Antonio, Tex.: Psychological Corporation, 1993.
- Fagan JF III, Singer LT, Montie JE, Shepherd PA. Selective screening device for the early detection of normal or delayed cognitive development in infants at risk for later mental retardation. *Pediatrics* 1986;78:1021-6.
- O'Doherty N. Neurological examination of the newborn: a routine for all. Hingham, Mass.: MTP Press, 1986.
- Dubowitz L, Dubowitz V. The neurological assessment of the preterm and full-term newborn infant. Vol. 79 of Clinics in developmental medicine. London: Spastics International Medical Publications, 1981.
- Precht HFR. The neurological examination of the full term newborn infant: a manual for clinical use from the department of developmental neurology, University of Groningen. 2nd ed. Vol. 63 of Clinics in developmental medicine. London: Spastics International Medical Publications, 1977.
- Paine RS, Oppé TE. Neurological examination of children. Vols. 20/21 of Clinics in developmental medicine. London: Spastics Society Medical Education and Information Unit in association with William Heinemann Medical Books, 1966.
- StatXact-Turbo: statistical software for exact nonparametric inference: user manual. Cambridge, Mass.: CYTEL Software Corporation, 1992.
- Treasure T, Naftel DC, Conger KA, Garcia JH, Kirklin JW, Blackstone EH. The effect of hypothermic circulatory arrest time on cerebral function, morphology, and biochemistry: an experimental study. *J Thorac Cardiovasc Surg* 1983;86:761-70.
- Clarkson PM, MacArthur BA, Barratt-Boyes BG, Whitlock RM, Neutze JM. Developmental progress after cardiac surgery in infancy using hypothermia and circulatory arrest. *Circulation* 1980;62:855-61.
- Subramanian S, Vlad P, Fischer L, Cohen M. Sequelae of profound hypothermia and circulatory arrest in the corrective treatment of congenital heart disease in infants and small children. In: Kidd BSL, Rowe RD, eds. The child with congenital heart disease at surgery. Mt. Kisco, N.Y.: Futura, 1976:421-31.
- Haka-Ikse K, Blackwood MJA, Steward DJ. Psychomotor development of infants and children after profound hypothermia during surgery for congenital heart disease. *Dev Med Child Neurol* 1978;20:62-70.
- Messmer BJ, Schallberger U, Gattiker R, Senning A. Psychomotor and intellectual development after deep hypothermia and circulatory arrest in early infancy. *J Thorac Cardiovasc Surg* 1976;72:495-502.
- Stevenson JG, Stone EF, Dillard DH, Morgan BC. Intellectual development of children subjected to prolonged circulatory arrest during hypothermic open heart surgery in infancy. *Circulation* 1974;50:Suppl II:II-54-II-59.

21. Wright JS, Hicks RG, Newman DC. Deep hypothermic arrest: observations on later development in children. *J Thorac Cardiovasc Surg* 1979;77:466-8.
22. Wells FC, Coghill S, Caplan HL, Lincoln C. 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.
23. Dickinson DF, Sambrooks JE. Intellectual performance in children after circulatory arrest with profound hypothermia in infancy. *Arch Dis Child* 1979; 54:1-6.
24. Jonas RA. Review of current research at Boston Children's Hospital. *Ann Thorac Surg* 1993;56:1467-72.
25. Gross SJ, Slagle TA, D'Eugenio DB, Mettelman BB. Impact of a matched term control group on interpretation of developmental performance in pre-term infants. *Pediatrics* 1992;90:681-7.
26. McConnell JR, Fleming WH, Chu WK, et al. Magnetic resonance imaging of the brain in infants and children before and after cardiac surgery: a prospective study. *Am J Dis Child* 1990;144:374-8.
27. Muraoka R, Yokota M, Aoshima M, et al. Subclinical changes in brain morphology following cardiac operations as reflected by computed tomographic scans of the brain. *J Thorac Cardiovasc Surg* 1981;81:364-9.
28. Gilles FH, Leviton A, Jammes J. Age-dependent changes in white matter in congenital heart disease. *J Neuropathol Exp Neurol* 1973;32:179. abstract.
29. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Acquired neuropathologic lesions associated with the hypoplastic left heart syndrome. *Pediatrics* 1990;85:991-1000.
30. Terplan KL. Patterns of brain damage in infants and children with congenital heart disease: association with catheterization and surgical procedures. *Am J Dis Child* 1973;125:176-85.
31. *Idem*. Brain changes in newborns, infants and children with congenital heart disease in association with cardiac surgery: additional observations. *J Neurol* 1976;212:225-36.
32. Volpe JJ. Hypoxic-ischemic encephalopathy: neuropathology and pathogenesis. In: Volpe JJ, ed. *Neurology of the newborn*. 3rd ed. Philadelphia: W.B. Saunders, 1995:279-313.
33. Lombroso CT, Holmes GL. Value of the EEG in neonatal seizures. *J Epilepsy* 1993;6:39-70.
34. Jensen FE, Applegate CD, Holtzman D, Belin TR, Burchfiel JL. Epileptogenic effect of hypoxia in the immature rodent brain. *Ann Neurol* 1991;29: 629-37.
35. Jensen FE, Holmes GL, Lombroso CT, Blume HK, Firkusny IR. Age-dependent changes in long-term seizure susceptibility and behavior after hypoxia in rats. *Epilepsia* 1992;33:971-80.
36. Jensen FE, Applegate CD, Burchfiel JL, Lombroso CT. Differential effects of perinatal hypoxia and anoxia on long term seizure susceptibility in the rat. *Life Sci* 1991;49:399-407.
37. Holmes GL. Do seizures cause brain damage? *Epilepsia* 1991;32:Suppl 5: S14-S28.
38. Ross G. Some thoughts on the value of infant tests for assessing and predicting mental ability. *J Dev Behav Pediatrics* 1989;10:44-7.
39. Ulvund SE. Predictive validity of assessments of early cognitive competence in light of some current issues in developmental psychology. *Hum Dev* 1984;27:76-83.
40. Ross G, Lipper EG, Auld PAM. Consistency and change in the development of premature infants weighing less than 1,501 grams at birth. *Pediatrics* 1985;76:885-91.