THE RELATIONSHIP BETWEEN INTELLIGENCE AND DURATION OF CIRCULATORY ARREST WITH DEEP HYPOTHERMIA

A total of 114 children (51 with tetralogy of Fallot, 30 with transposition of the great arteries, and 33 with ventricular septal defect) who had these defects repaired with the use of deep hypothermia and circulatory arrest were assessed for intellectual and neuropsychologic function at an average of 9 to 10 years after the operation. Children with preoperative intellectual handicaps or postoperative neurologic complications were excluded. These children were compared with 54 who had atrial septal defects repaired with the use of cardiopulmonary bypass. The only significant difference in the neuropsychologic measures was that the bypass group had reaction times 2 to 3 seconds shorter on average than those of the hypothermic circulatory arrest group. Although there was no significant difference in intelligence quotient between the groups, a relationship between intelligence quotient and arrest time was found. Regression analysis of intelligence quotient against duration of arrest showed a significant decrease in intelligence quotient with increasing arrest time (slope = -0.36 ; $p = 0.002$; 95% confidence interval, $-0.59, -0.14$) indicating a decrease of 3 to 4 intelligence quotient points for each extra 10 minutes of arrest time. It appears that deep hypothermia with circulatory arrest for cardiac operations in children does not fully protect the brain, with a linear relationship existing between the amount of impairment and the duration of circulatory arrest. (J THORAC CARDIOVASC SURG 1995;110:786-92)

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In 1953 Lewis and Taufic¹ reported the successful closure of an atrial septal defect (ASD) in a 5-year-old child with the use of surface cooling followed by cessation of circulation for 5½ minutes. The original technique was severely limited by the apparent safe time of circulatory arrest, but the principle was later extended by the reduction of brain temperatures to 20° C or lower to permit extended periods of circulatory arrest.² The report by Björk and Hultquist³ that five patients had gross neurologic damage after cardiac operations that used this technique led to its abandonment for

clinical operations for several years. However, the practical difficulties with conventional cardiopulmonary bypass, especially for complex defects and in small infants, stimulated refinements of the method⁴⁻⁸ and successfully opened the field of reparative surgery in neonates and infants.

Studies with dogs showed that their brains tolerate up to 60 minutes of a total lack of circulation at a temperature of 20° C without any obvious signs of cerebral damage.^{9, 10} These animal studies formed the basis for the view that up to 60 minutes of circulatory arrest at 20° C is safe. The technique has considerable advantages, inasmuch as it offers almost ideal operating conditions with a still, relaxed, and bloodless heart. More recent studies by Treasure and colleagues¹¹ that exploited the arterial anatomy of the golden hamster have shown that the "safe" period of circulatory arrest in that preparation is 30 minutes and possibly up to 45 minutes.

The results of clinical studies of whether cerebral anoxia with hypothermia is consistent with normal neurologic outcome have been conflicting. A study of 38 children up to 6 years after deep hypothermia and circulatory arrest showed a normal distribution

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of intelligence quotient (IQ) values and no correlation with the duration of circulatory arrest.¹² Two studies that used control groups also did not show adverse effects.^{13, 14} In contrast, Wells and colleagues,¹⁵ with the use of sibling control subjects and control subjects who had cardiac operations with the use of cardiopulmonary bypass, showed a fall in IQ in a group of 31 children who underwent hypothermia with a variety of lesions, which was directly related to the duration of the circulatory arrest, particularly with circulatory arrest times greater than 45 minutes. Recent evidence from Bellinger and colleagues¹⁶ suggests that the problem may not have so much to do with the duration of deep hypothermic circulatory arrest, but with the rate of cooling, with an association between shorter cooling periods and subsequent slower development.

Evidence that the degree of increase in levels of creatine kinase isoenzyme BB, a specific marker of brain ischemia, is directly related to duration of arrest time in the presence of hypothermia¹⁷⁻¹⁹ has raised concern about the safety of this technique. Animal studies of phosphorus 31-nuclear magnetic resonance spectroscopy show circulatory arrest with hypothermia results in depletion of high-energy phosphates,²⁰ and cerebral flow studies in children show an impairment of cerebral reperfusion after hypothermia and circulatory arrest.²¹

The aim of this study was to review results in a large group of children who had deep hypothermia and circulatory arrest and who are now old enough for accurate psychologic and neuropsychologic testing to see whether there is an association between the various measures of cognitive functioning and the duration of total circulatory arrest.

Methods

Study population. The study population consisted of all children operated on in infancy at The Children's Hospital, Camperdown, for transposition of the great arteries (TGA), tetralogy of Fallot (TOF), or ventricular septal defect (VSD) during the period 1972 to 1982 with use of the technique of profound hypothermia and circulatory arrest and who were between 7 and 15 years old at the time of review. The operations were performed by the same surgical team with surgical and anesthetic techniques remaining constant during this period. Our technique has been described previously²² and emphasized slow core cooling with high-flow cardiopulmonary bypass at a rate of 2.4 L/min per square meter of body surface area. Perfusate temperature at the beginning of perfusion was 30° C, and the temperature gradient between nasopharyngeal and blood temperatures was kept less than 8° C for a minimum of 20 minutes of cooling to reduce

nasopharyngeal temperature to 18° to 20° C. When the core temperature, as reflected by nasopharyngeal temperature, was stabilized at the required level, the ascending aorta was clamped to induce cardiac arrest. Chemical cardioplegia was not used in this era. The extracorporeal pump was stopped and venous blood allowed to drain freely into the oxygenator before the venous line was clamped. Cannulas were removed temporarily only if needed for access. On completion of the repair, cardiopulmonary bypass was resumed and rewarming effected with use of the extracorporeal heat exchanger and also a water blanket at 35° C. When blood temperature reached 30° C arterial acid-base studies were done and significant acidosis corrected by infusion of sodium bicarbonate before cessation of extracorporeal circulation. Diligent efforts were made to exclude air, including displacement with saline solution during heart closure, often needle aspiration, and creation of a stab hole in the ascending aorta, which was left bleeding freely until the heart was ejecting vigorously after separation from bypass. During this era the so-called alpha-stat principle was not followed. The oxygenator was ventilated with 2.5% CO₂ in 97.5% O₂ at the beginning of bypass and the inspired carbon dioxide fraction increased to 5% during cooling. The aim was to maintain pH and carbon dioxide tension in a "normal" range when corrected for temperature. During rewarming the inspired carbon dioxide fraction reverted to 2.5%.

These operative and anesthetic data for each case were extracted from the record including the duration of cessation of cerebral circulation. We excluded all children identified from the clinical records as having preoperative intellectual handicaps (such as syndromes associated with intellectual handicap or delayed milestones as a result of perinatal hypoxic events), any children who had postoperative complications likely to affect development such as cerebrovascular accident or seizures, and any who had moved interstate or overseas. Children who had transient postoperative dystonic movements and those who had low cardiac output after repair without other complications were not excluded. Routine electroencephalographic testing was not done.

One hundred forty surviving children were eligible for participation in the study. Of this group 16 could not be found and 10 declined to join the study, leaving 114 subjects (81% response rate). There were 30 children who had TGA, 51 who had TOF, and 33 with VSD. The characteristics of these children are shown in Table I. All children were in good health at the time of review with no restrictions on their physical activity and were attending mainstream schools.

Control group. In an attempt to control for possible confounding effects of cardiopulmonary bypass alone we chose a control group of 54 children who underwent operation in the same period for ASD with cardiopulmonary bypass but without profound hypothermia or circulatory arrest. The characteristics of these children are shown in Table I. Socioeconomic status of the child's family was measured according to a six-point scale used for determining social class in Australia.²³ Informed consent was obtained from all subjects and the study was

Table I. Characteristics of subjects by diagnostic group

Characteristic	Diagnostic group			
	TGA (n = 30)	TOF (n = 51)	VSD (n = 33)	ASD (n = 54)
No. of male subjects (%)	24 (80%)	29 (57%)	22 (67%)	25 (46%)
Age at operation (mo)*	7.5 (5-9)	23 (13-37)	11 (6-21)	48 (34-52)
Age at review (yr)	10.1 (2.3)	10.9 (2.2)	10.7 (2.7)	10.4 (2.1)
Duration of arrest (min)	45 (10)	46 (11)	42 (11)	—
Socioeconomic status*	4 (3-6)	5 (4-6)	5 (3.5-6)	5 (4-6)
IQ				
Full scale	100 (17)	100 (13)	102 (12)	101 (14)
Verbal scale	99 (19)	98 (13)	102 (14)	101 (15)
Performance scale	101 (15)	102 (15)	102 (13)	100 (14)

Mean values given with standard deviation in parentheses (except for number of male subjects).

*Median (interquartile range) shown because distributions are skewed.

approved by the Ethics Committee of the Children's Hospital.

Assessment. At least one parent was interviewed to obtain information about family social and educational background and general health. All children were assessed with the Wechsler Intelligence Scale for Children (WISC-R),²⁴ which gives full-scale, performance, and verbal intelligence quotients. The 11 subtests of the WISC-R can be further divided into three groups: verbal comprehension, perceptual organization, and freedom from distractibility.²⁵

Six neuropsychologic measures were used as follows:

1. The Rey-Osterrieth Complex Figure, to assess perceptual organization and visual memory,²⁶ in which the child is asked first to copy the figure and then to draw the same figure from memory 30 minutes later. It is considered an effective method of investigating nonverbal memory.²⁷
2. Reaction Time, a sensory reaction test in three parts in which the child is asked to press a button in response to a light, a buzzer, and randomized presentation of the light or the light plus the buzzer. The test is scored in reaction response times in seconds.
3. Controlled Oral Word Association Test, a test of verbal fluency in which the child is asked to generate lists of words beginning with particular letters.²⁶ Patients with frontal lesions have lower fluency scores than control subjects on this measure.²⁸
4. Stroop Color and Word Test, which has been shown to effectively differentiate between brain-damaged and control subjects²⁹ by measuring the ease with which the child can shift from one perceptual set to another.²⁶
5. Trail Making Test of visual conceptual and visuomotor tracking involving motor speed and attention.²⁶ This has been shown to be a reliable indicator of the presence of brain damage.³⁰
6. Selective Reminding Test, a method of evaluating memory in which the subject is asked to recall as many words as possible from a list that has just been read to the subject. The scoring method allows differences to be analyzed between retention, retrieval, and long-term storage in memory.³¹

Many of these test results are dependent on age, sex, or socioeconomic status. Because standardized scores for

these neuropsychologic measures are not available, a reference group of 51 school children was tested under similar conditions. These children were of similar age range (mean age 11.6 years, standard deviation 2.6 years) and socioeconomic status to those who had previously had cardiac operations, and they had been free of major illness or surgery. Data from these 51 children were used to establish the linear regression dependency of each of the neuropsychologic measures on age, sex, and socioeconomic status unconfounded by possible unknown effects of cardiac defect. All the measurements for the patients with cardiac operations were then adjusted to standard age, sex, and socioeconomic status with use of the relevant regression equation derived from the reference group. Some variables needed to be transformed by taking logarithms (for trail making times) or square roots (for Rey-Osterrieth figure copy time) to make their distribution closer to normal. Means of adjusted variables were compared by *t* tests or Mann-Whitney tests if transformation to normality was not possible (for Selective Reminding and Reaction Time tests). The IQ scores, which are already standardized for age and do not differ by sex, were not further adjusted for socioeconomic status. Although there was a strong association between IQ and socioeconomic status, there was no confounding effect of socioeconomic status because its mean score was similar in all groups (cyanotic 4.54, acyanotic 4.58, ASD 4.56).

The following comparisons between groups were made, with groups combined as shown unless the preceding test indicated a significant difference: TGA versus TOF; (TGA + TOF) (cyanotic) versus VSD (acyanotic); (TGA + TOF + VSD) (hypothermic arrest) versus ASD (normothermic perfusion). Two-sided *p* values less than 0.05 were regarded as statistically significant. Linear regression was used to determine the effect of arrest time on IQ. The correlation between arrest time and neuropsychologic measures, adjusted for age, sex, and socioeconomic status, was investigated with use of either Pearson's or Spearman's rank correlation as appropriate.

Results

A comparison of full-scale, verbal, and performance IQ scores among the four groups did not show any significant differences (Table I). Adjusted

Table II. Relationship between Wechsler IQ and duration of circulatory arrest with hypothermia

	Regression slope	p Value
Full-scale IQ	-0.36	0.002
Verbal IQ (subtests 1-5)	-0.33	0.013
Performance IQ (subtests 7-11)	-0.33	0.009
Subtests		
1. Information	-0.055	0.01
2. Similarities	-0.065	0.03
3. Arithmetic	-0.065	0.02
4. Vocabulary	-0.050	0.05
5. Comprehension	-0.026	0.16
6. Digit span	-0.012	0.66
7. Picture completion	-0.023	0.28
8. Picture arrangement	-0.028	0.30
9. Block design	-0.097	0.0004
10. Object assembly	-0.076	0.008
11. Coding	-0.013	0.60
Verbal communication (subtests 1, 2, 4, 5)	-0.21	0.02
Perceptual organization (subtests 7, 8, 9, 10)	-0.22	0.005
Freedom from distractibility (subtests 3, 6, 11)	-0.09	0.14

auditory reaction time for the dominant hand was found to be significantly greater in the TGA group than in the TOF group ($p = 0.006$). Because this was the only significant difference between the two cyanotic groups for the neuropsychologic measures, including the other three reaction time variables, results for the TGA and TOF groups were pooled. Further comparisons with this cyanotic group for auditory reaction time for the dominant hand will be conservative because of the heterogeneity between the TGA and TOF groups.

There were no significant differences between the cyanotic (TGA + TOF) and cyanotic (VSD) groups on any of the neuropsychologic measures. We were then able to pool the results for all three hypothermic groups and compare them with those for the bypass (ASD) group. There were no significant differences between the hypothermic circulatory arrest groups and the bypass group on any of the neuropsychologic measures except for reaction time. The bypass group had significantly shorter reaction times on all four tests: for visual reaction with the dominant hand ($p = 0.02$) and the nondominant hand ($p = 0.009$) and auditory reaction with the dominant ($p = 0.006$) and nondominant ($p = 0.03$) hands. The estimated difference in the median re-

Fig. 1. Relationship between IQ and arrest time: $IQ = 116.7 - 0.36 \times \text{arrest time (minutes)}$ ($p = 0.002$, $R^2 = 0.08$, standard error of regression = 13.1). Asterisks, TGA operation group; triangles, TOF operation group; squares, VSD operation group.

action times was 2 or 3 seconds, which is equivalent to 2 or 3 years of age.

Relationship between IQ and arrest time. This relationship was examined for the 114 children (51 TOF, 30 TGA, 33 VSD) who had circulatory arrest with hypothermia. There was a significant decrease in full-scale IQ with increased arrest time ($p = 0.002$). The slope of the regression line of -0.36 (95% confidence interval, $-0.59, -0.14$) indicates a decrease of 3 to 4 IQ points for each 10 minutes of arrest time. The slopes did not differ among the three groups ($F_{2,108} = 0.52$, $p = 0.59$). This decreased IQ with increased arrest time was similar for the verbal IQ scores (slope = -0.33 , $p = 0.01$) and performance scores (slope = -0.33 , $p = 0.009$) (Fig. 1).

When the 11 subtests of the Wechsler scale were plotted against arrest time, there were significant effects on block design ($p = 0.0004$) and object assembly ($p = 0.008$), which are two of the five components of performance IQ, and on information ($p = 0.01$), similarities ($p = 0.03$), arithmetic ($p = 0.02$), and vocabulary ($p = 0.05$), which are four of the five components of verbal IQ (Table II). Group-

ing the subtests into verbal communication (subtests 1, 2, 4, 5), perceptual organization (subtests 7, 8, 9, 10), and freedom from distractibility (subtests 3, 6, 11) showed significant effects on perceptual organization ($p = 0.005$) and verbal communication ($p = 0.02$).

There was no correlation between any of the adjusted neuropsychologic measures and arrest time.

Discussion

The earlier studies on intelligence and development of children after the use of profound hypothermia to repair cardiac defects suggested that there was little or no impairment^{12-14, 32-35} and no correlation between arrest time and intellectual development.^{12-14, 33} However these studies had small numbers, subjects with a variety of cardiac lesions, and short follow-up periods so that neuropsychologic measures and intelligence tests with good predictive value were not usually able to be done.

The duration of a safe time for cardiac arrest and cessation of cerebral circulation with the use of hypothermia has remained a topic of controversy. Animal studies with this technique have shown that some cerebral damage can occur after 30 minutes¹¹ although estimates of the safe period for infants vary from 45 to 60 minutes.^{15, 36} The evidence that the level of creatinine kinase isoenzyme BB rises with increasing duration of arrest shows that some cerebral damage does occur although it has not been clear whether this leads to ongoing cerebral impairment.

Our study looked at a large number of children who were operated on in the same surgical unit by a constant team with a standardized technique, compared the development of children with different types of cardiac defects, and assessed the children's development at an age when extensive psychologic and neuropsychologic assessment can be done with accuracy. We found no difference in overall IQ scores between the hypothermic and bypass groups and no difference on neuropsychologic measures except for reaction time in which the group of children who had bypass, rather than hypothermia, had significantly faster reaction times. More important, there was a definite relationship between lower IQs and longer periods of hypothermic arrest, with no evidence of a safe period for arrest.

Ideally, in a study of this nature, preoperative and postoperative measures of intellectual function should have been used. The young age at which corrective operation is done and the lack of psycho-

logic measures that have strong predictive value when used in infancy, particularly when subtle differences are being sought, rule out such a study. We have attempted to account for adverse effects of the preoperative disease state, including hypoxemia, by comparing cyanotic with noncyanotic groups and to control for any possible adverse effect of cardiopulmonary bypass alone by comparing the profound hypothermia and circulatory arrest groups with a group undergoing ASD repair with continuous cardiopulmonary bypass. It is recognized that this control is also imperfect, in that the clinical state was less severe, the operation at a later age and simpler, and the duration of cardiopulmonary bypass less.

Although there does appear to be a definite relationship between duration of hypothermic arrest and intellectual function as measured by the WISC-R, the effects are not major, and this may be a factor accounting for the equivocal results of the smaller, earlier studies. However, these findings suggest that some of the results of cerebral anoxia and poor perfusion that have been documented immediately after hypothermic arrest¹⁷⁻²¹ do become manifest as intellectual difficulties that can be detected 9 to 10 years after operation. A strategy to reduce this risk that we now use extensively is to plan the operative steps to do as much as possible of the repair during cooling or rewarming perfusion, minimizing the period of complete circulatory arrest. Another alternative used since the children in this study were operated on involves prolonged periods of perfusion at low flow and low body temperature,³⁷ which affords some of the advantages of circulatory arrest but at the cost of a more cluttered operative field and consequent prolonged perfusion and myocardial ischemic times. The results of this study suggest that it may be wise to exercise caution in the use of deep hypothermia and circulatory arrest when other techniques or modifications can be used without prejudicing the quality or safety of the surgical repair.

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