SURGERY FOR CONGENITAL HEART DISEASE

BENEFIT OF NEUROPHYSIOLOGIC MONITORING FOR PEDIATRIC CARDIAC SURGERY

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Background. Pediatric patients undergoing repair of congenital cardiac abnormalities have a significant risk of an adverse neurologic event. Therefore this retrospective cohort study examined the potential benefit of interventions based on intraoperative neurophysiologic monitoring in decreasing both postoperative neurologic sequelae and length of hospital stay as a cost proxy. **Methods:** With informed parental consent approved by the institutional review board, electroencephalography, transcranial Doppler ultrasonic measurement of middle cerebral artery blood flow velocity, and transcranial near-infrared cerebral oximetry were monitored in 250 patients. An interventional algorithm was used to detect and correct specific deficiencies in cerebral perfusion or oxygenation or to increase cerebral tolerance to ischemia or hypoxia. **Results:** Noteworthy changes in brain perfusion or metabolism were observed in 176 of 250 (70%) patients. Intervention that altered patient management was initially deemed appropriate in 130 of 176 (74%) patients with neurophysiologic changes. Obvious neurologic sequelae (i.e., seizure, movement, vision or speech disorder) occurred in five of 74 (7%) patients without noteworthy change, seven of 130 (6%) patients with intervention, and 12 of 46 (26%) patients without intervention ($p = 0.001$). Survivors' median length of stay was 6 days in the no-change and intervention groups but 9 days in the no-intervention group. In addition, the percentage of patients in the no-intervention group discharged from the hospital within 1 week (32%) was significantly less than that in either the intervention (51%, $p = 0.05$) or no-change (58%, $p = 0.01$) groups. On the basis of an estimated hospital neurologic complication cost of \$1500 per day, break-even analysis justified a hospital expenditure for neurophysiologic monitoring of \$2142 per case. **Conclusions:** Interventions based on neurophysiologic monitoring appear to decrease the incidence of postoperative neurologic sequelae and reduce the length of stay. Inasmuch as the break-even cost for neurophysiologic monitoring is more than four times the actual average charge, both patients and hospital may profit from this service. Because this study was not a truly randomized clinical trial, unintentional statistical bias may have occurred and caution is urged in interpreting the magnitude of apparent intergroup outcome differences. (J Thorac Cardiovasc Surg 1997;114:707-17)

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Over the past several years, our group has used multimodality neurophysiologic monitoring to identify the specific causes of neurologic injury associated with the diagnoses or surgical correction of cardiac dysfunction. We¹ demonstrated the reliable detection of cerebral ischemia by quantitative electroencephalography (EEG), transcranial Doppler (TCD) ultrasonography, and cerebral oximetry during the testing of implantable cardioverter-defibrillators. Additionally, our prospective controlled study² showed the potential clinical value of detecting cerebral ischemia during myocardial revascularization. Monitored patients had a significantly lower incidence of postoperative disorientation. Recently, we³ developed a neurophysiologic monitoring-based intervention algorithm to detect and correct sources of cerebral injury during cardiopulmonary bypass. The algorithm was initially successfully evaluated in high-risk adult cardiac operations for repair of aortic aneurysms with the aid of deep hypothermia and retrograde cerebral perfusion.⁴

The present report describes a retrospective examination of the clinical and economic benefit of this algorithmic approach to neurologic protection. The examination focused on pediatric patients having cardiac operations, partly because of their high susceptibility to brain injury.⁵ We⁶ had previously demonstrated the feasibility of intraoperative neurophysiologic monitoring in these young patients.

Methods

Patients. From June 1995 through December 1996, 250 pediatric patients underwent neurophysiologic monitoring during repair of congenital cardiac defects. Composition of the patient population is described in Table I. Essentially all patients undergoing cardiac surgery (open or closed) were monitored with the exception of those undergoing isolated closure of patent ductus arteriosus. This group was excluded because the extremely low incidence of neurologic complications did not appear to justify the additional expense of neurophysiologic monitoring.

Anesthetic and perfusion management. The standardized anesthetic protocol consisted of an opioid-midazolam infusion supplemented by bolus administration of these agents when indicated. The unique aspects of perfusion management were the following. Cranial (i.e., tympanic) temperature was maintained at one of three levels, 34°, 26°, or 18° C, depending on the surgical requirements. The rates of cooling and rewarming were standardized at 0.3° C/min. The lowest acceptable sustained blood pressure was determined by neurophysiologic monitoring, but in no case was it less than 30 mm Hg. Pump priming volumes were 650 ml for patients weighing less than 8 kg, 850 ml for patients weighing 8 to 14 kg, and 1200 ml for those weighing more than 14 kg. Larger patients had a nonblood prime (100 to 150 ml albumin 25%, electrolyte

Table I. Age distribution of pediatric patients undergoing cardiac operations

Age	No change		Intervention		No intervention	
	No.	%	No.	%	No.	%
<7 days	7	9	3	23	6	13
8-30 days	8	11	6	5	1	2
30 days-1 year	15	20	43	33	12	26
1-5 years	19	26	27	21	15	33
>5 years	25	34	24	18	12	26

solution [Normosol-R], and mannitol 0.5 to 1 gm/kg). Infant prime also contained 1 unit of fresh frozen plasma and 1 unit of packed red blood cells as needed to maintain a hematocrit value of 25%. Initial pump flow rates were set at 3.0 times the cardiac index for patients weighing less than 10 kg. Rates were changed proportionately in larger children to an ultimate value of 2.4 times the cardiac index. Alpha-stat acid-base management was used. On the basis of blood gas samples collected every 20 to 30 minutes, fresh gas flow through the membrane oxygenator was adjusted to maintain arterial carbon dioxide tension near 35 mm Hg. A Terumo Capiox combination membrane oxygenator-venous reservoir (Terumo Medical Corp., Somerset, N.J.) was used in conjunction with a Gish 40 μ m arterial line filter (Gish Biomedical, Inc., Irvine, Calif.). After periods of circulatory arrest, resumption of cold perfusion at the arrest temperature for 10 minutes preceded rewarming. In cases involving circulatory arrest, alpha-adrenergic blockade was used, which consisted of the administration of phentolamine 0.15 mg/kg before the onset of bypass and again during rewarming.

EEG. All neurophysiologic monitoring was performed by a dedicated technologist (H.L.E., V.S., G.N., A.S.). Cerebrocortical function was objectively characterized by using four-channel quantitative EEG. Cerebral biopotentials were recorded with gold cup electrodes placed at the Fp1-T3, Fp2-T4, C3-O1, and C4-O2 sites of the International 10-20 electrode placement system. Fourier spectral analysis of the EEG (A-1000, Aspect Medical Systems, Natick Mass.; or Excel Signal Analyzer, Cadwell Labs, Kennewick, Wash.; or NeuroTrac II, Moberg Medical, Ambler, Pa.) produced simple numeric indices suitable for characterizing changes in the complex waveforms. Amplitude of the signal was determined by total power in picowatts or decibels in successive 2-second epochs. A suppressed EEG was defined as an amplitude of less than 10 pW or 50 dB (i.e., signal-to-noise ratio of < 10:1) in more than 30% of epochs per minute. Excessive EEG slowing was defined as the relative delta (1.5 to 3.5 Hz) power band comprising more than 80% of the total power in the EEG signal.

Cerebral blood flow velocity measurement. Flow through the right middle cerebral artery was verified continuously and noninvasively by TCD ultrasonography. A 2 MHz pulse-wave ultrasound transducer was fixed above the zygomatic arch with a commercially available soft rubber holder (Medasonics, Inc., Fremont, Calif.). This transducer insonated the portion of the middle

Table II. Intervention algorithm initiated by EEG slowing and/or cerebral venous oxygen desaturation

<i>Temp</i>	<i>BP</i>	<i>TCD</i>	<i>Notification</i>	<i>Intervention</i>
Prebypass				
0	0	–Peak velocity	Aorta obstructed	Adjust aortic cannula
0	0	–Diastolic velocity	Cava obstructed	Adjust venous cannula
Cardiopulmonary bypass				
0	0	+ Peak velocity	Hyperemia	–Pump flow
0	0	Gas emboli	Gas emboli	Deair; repair circuit
+	0	–Peak velocity	Flow-metabolism uncoupling	+BP; –Metabolic demand
0	0	–Peak	Cerebral flow low	Adjust cannula/clamp; +Pump flow
Postbypass				
0	0	–Diastolic velocity	Cerebral edema	Mannitol; Ultrafiltration
Anytime				
0	–	–Peak velocity	Dysautoregulation	+ BP; neuroprotectant
With + EEG frequency				
0	0,+	0,+ peak velocity	Insufficient anesthesia	+ Anesthesia

0, No change; +, increase; –, decrease; BP, blood pressure; TCD, transcranial Doppler; Temp, tympanic or nasopharyngeal temperature.

cerebral artery near its juncture with the ipsilateral anterior cerebral artery. A color Fourier analyzer (Neuro-Guard, Medasonics) displayed the flow velocity spectral profile on a color monitor. Key spectral segments illustrating changes in cerebral blood flow velocity were also stored digitally and printed as black and white images. Cerebral blood flow velocity was quantified from the upper edge of the velocity spectrum. A reversal of flow direction was signified by spectral inversion. The criterion for a noteworthy decrease in peak flow velocity was an absolute value of 20 cm/sec for large children or a 50% reduction from baseline for neonates and infants. The baseline was established just before insertion of the aortic cannula. An excessively high peak velocity indicative of hyperemia was defined as a value twice the baseline that persisted for more than 3 minutes. The criterion for a low diastolic velocity was a velocity below the level of detectability (i.e., 4 cm/sec with a 75 Hz low-pass filter).

Regional cerebral venous oxygen saturation measurement. The adequacy of cerebral oxygenation was assessed with the use of relative changes in cerebrovenous oxygen saturation with transcranial near-infrared spectroscopy. A self-adhesive patch, containing an infrared light-emitting diode and two distant sensors (30 mm [scalp] and 40 mm [scalp plus brain]), was fixed on the left side of the patient's forehead. Cerebrovenous oxygen saturation was calculated from the differential signal obtained from these two sensors, expressed as the venous-weighted percent oxygenated hemoglobin. The cerebrovenous oxygen saturation trend was displayed on an infrared spectrophotometer (INVOS 3100A, Somanetics Corp., Troy, Mich.). A specially designed preamplifier attenuated the sensor output tenfold to prevent amplifier saturation by the high-amplitude signals. The trend represented a temperature-corrected average of 16.5 seconds of data updated every 3.3 seconds. Data points comprising the moving average trend were stored continuously on floppy disk every 30 seconds.

Desaturation signifying cerebral ischemia was defined as a regional cerebral venous oxygen saturation decrease

of more than 20% of the baseline established just before aortic cannulation, which persisted for more than 3 minutes. The 20% value had been determined empirically from our earlier study of the cerebral ischemia associated with implantable cardioverter-defibrillator testing in normothermic unanesthetized adults.¹

Each patient's head was rotated leftward to improve surgical exposure and central venous line access. After positioning, a metal shelf was placed just above the head to protect the face and airway. The head position and shelf made it nearly impossible to fix and adjust an ultrasound probe placed over the left temporal region. Thus, to ensure some monitoring of both cerebral hemispheres during hypothermic suppression of EEG activity, we placed the oximeter sensor on the left side of the forehead.

Neurophysiologic monitoring algorithm. The goals of neurophysiologic monitoring were to detect potential problems in patient management and to assess response to intervention. Specific problems fell primarily into one of three general areas: (1) abnormalities in cerebral perfusion, (2) cerebral venous oxygen desaturation, and (3) insufficient anesthetic depth. The algorithm for intervention, which was previously developed for use in adult cardiac surgery,³ is summarized in Table II. The same intervention criteria were used in all cases. Detection of a perfusion abnormality was based on TCD evidence of low or absent flow velocity coupled with an EEG indication of synaptic depression or a cerebrovenous oxygen desaturation, or both. In the second group a noteworthy decrease in cerebral venous oxygen saturation occurred without a noteworthy change in TCD flow velocity. With inadequate anesthetic delivery, signs of increased synaptic activity and TCD flow velocity were coupled with a decreasing cerebrovenous oxygen saturation resulting from enhanced neuronal metabolic activity. In some cases, if adjustments in patient management failed to correct deficient perfusion or oxygenation, neuroprotectants were administered in the hope of increasing the brain's tolerance to ischemia/hypoxia. The neuroprotectant combination was phenytoin

Table III. Number of primary potential problems detected by neurophysiologic monitoring

Problem	Intervention	No intervention
Perfusion imbalance		
Peak flow velocity high (hyperemia)	3	0
Peak velocity low (aortic obstruction; low pump flow or pressure)	28	6
Doppler signal absent (no cerebral flow)	2	0
Diastolic velocity low (venous obstruction; edema)	4	4
Gas emboli	12	6
Cerebral venous oxygen desaturation		
Airway obstruction	1	0
Hemoglobin low	3	2
Fio ₂ low	5	0
Carbon dioxide low	1	0
Arterial pressure or pump flow low	18	41*
Cerebral hypermetabolism with rewarming	10	11†
Cardiac output low	2	3
Insufficient anesthetic depth		
EEG frequency increase	6	2
Insufficient cooling		
EEG activity with deep hypothermia	1	0

Fio₂ Inspired oxygen fraction.**p* < 0.001 compared by differences in proportions.†*p* < 0.01 compared by differences in proportions.

15 mg/kg and dexamethasone 0.15 mg/kg. Because the propylene glycol-solubilized phenytoin formulation may induce cardiac dysfunction and profound hypotension, it was administered only as a last resort in hemodynamically stable patients. The specific problems detected and associated interventions are shown in Tables III and IV.

Postoperative care. Postoperative sedation for all patients was standardized under the direction of a single surgeon (E.H.A.). It included a fentanyl infusion supplemented with bolus doses of midazolam when indicated. Routine neurologic assessments were performed daily by the neonatal or pediatric intensivists. Suspected neurologic events were confirmed subsequently by a pediatric neurologist (M.K.S.) and the adverse outcomes were documented for inclusion in our database by cardiac nurse clinicians (C.D.C., K.M.C.).

Study design and statistical analysis. Neurophysiologic monitoring technologists recorded the following physiologic measures every 5 minutes throughout each case in a computerized spreadsheet: mean arterial pressure, central venous pressure, end-tidal anesthetic concentration, tympanic temperature, cerebral venous oxygen saturation, the EEG parameters of relative delta power and burst-suppression ratio, the minimum, mean, and maximum middle cerebral artery flow velocities, and the cumulative cerebral microemboli count. In addition, a 100-field computerized database of relevant demographic, diagnostic, intraoperative, and postoperative data was maintained on all pediatric patients undergoing cardiac operations. These two

Table IV. Interventions guided by neurophysiologic monitoring

Intervention	No. of cases
Perfusion imbalance	
Correct mechanical obstruction	
Aortic cannula reposition	22
Venous cannula reposition	3
Vascular clamp reposition	3
Additional deairing; repair air leak	7
Pump flow increase	15
Pump flow decrease	3
Plasma volume expansion	4
Return to cardiopulmonary support	6
Blood pressure increase	29
Carbon dioxide increase	2
Deficient oxygenation	
Increase Fio ₂	5
Transfuse whole blood	3
Reintubate	1
Insufficient anesthetic depth	
Increase anesthetic delivery	8
Limited ischemia tolerance	
Neuroprotectant	18
Additional cooling	1

digital records formed the basis of the retrospective review. To limit the database to a manageable size, we recorded only the most significant monitoring event and response.

The application of multimodality neurophysiologic monitoring began primarily as an observational study without the intention to intervene with every noteworthy change. As experience accrued and the surgical team analyzed the cumulative database results, the value of responding to neurophysiologic monitoring detections became increasingly apparent. After several of these interim analyses, most noteworthy changes were followed with an appropriate intervention (Fig. 1). As such, the total group of patients could be divided into three cohorts based on the presence or absence of a noteworthy neurophysiologic change (i.e., notification and no change) and the response of the surgical team to the notification (i.e., intervention and no intervention). This design allowed us to examine the consequences of neurophysiologic change versus no change and intervention versus no intervention.

The central tendency and dispersion of Gaussian interval data were described by the mean and 95% confidence interval, and the median and interquartile ranges were used for non-Gaussian data. Ordinal (scalar) values and non-Gaussian interval data were expressed as proportions or odds ratios (i.e., percent affected with 95% confidence intervals). The confidence intervals for binomial proportions were calculated with the aid of personal computer-based StatXact software (Cytel Software, Cambridge, Mass.). Unless otherwise indicated, all numbers in parenthesis signify 95% confidence intervals.

Financial decisions profoundly affecting health care are often not based on statistical comparisons commonplace

Fig. 1. Time line of cases in which noteworthy neurophysiologic monitoring changes were observed. As experience accrued, virtually all noteworthy detections resulted in an intervention.

in scientific literature. That is, statistical and financial significance are not necessarily synonymous or related. Therefore a conventional break-even analysis was used to determine the revenue-neutral hospital expenditure for neurophysiologic monitoring justified by the reduced rate of neurologic complications and decreased length of stay. The hospital's daily cost for a neurologic complication or prolonged stay was estimated to be \$1500 per day.

Results

Patient characteristics. The clinical characteristics of the three groups are summarized in Tables I and V. There were no marked intergroup differences in age distribution or primary surgical procedure. The distribution of neurophysiologic monitoring notifications was similar in both the intervention and no-intervention groups (Fig. 2). The TCD and cerebral oximetric criteria for deterioration were established with the use of baseline reference values obtained just before aortic cannulation. Thus the criteria were dependent, in part, on the cerebral state at that moment. Therefore intergroup comparisons of several physiologic measures were made to detect evidence of unintentional statistical bias resulting from nonrandom group assignment. Group mean and 95% confidence intervals for the no-change, intervention, and no-intervention groups, respectively, were as follows: mean arterial pressure, 58 mm Hg (54 to 61 mm Hg), 54 mm Hg (46 to 54 mm Hg), and 52 mm Hg (45 to 58 mm Hg); end-tidal carbon dioxide, 29 mm Hg (27 to 31 mm

Table V. Distribution of surgical procedures and neurologic sequelae

Procedure	No change	Intervention	No intervention
Aortic arch repair		4	
Aortic stenosis repair		11	2
Arterial switch	3	4	1
ASD closure	12	12	5
AV canal repair	2	8	3
Valve repair/replacement	3	4	2
Blalock-Taussig shunt	3	9	2
Coarctation of aorta	10	9	2
DORV repair			2
Fontan	1	3	2
Glenn shunt (bidirectional)	3	6	3
Miscellaneous	12	2	1
Myectomy	2	1	
Norwood		9	2
Pul stenosis/atresia repair	1	11	
PAPVR or TAPVR repair	2	4	3
Rastelli		1	1
Ross	6	6	2
Tetralogy of Fallot repair	3	4	4
Truncus arteriosus repair		2	1
Transplant, cardiac	1	1	
VSD repair	10	19	1
TOTAL	74	130	46
Neurologic sequelae	5	7	12
Deaths	5	8	17

ASD, Atrial septal defect; AV, atrioventricular; DORV, double-outlet right ventricle; PAPVR, TAPVR, partial or total anomalous pulmonary venous return; VSD, ventricular septal defect.

Fig. 2. Distribution of type of neurophysiologic monitoring change observed in the intervention and no-intervention groups.

Hg), 30 mm Hg (28 to 32 mm Hg), and 31 mm Hg (28 to 34 mm Hg); tympanic temperature, 35° (34° to 36°), 35° (35° to 36°), and 35° (34° to 36°). In the absence of significant intergroup differences, no evidence of bias was found.

Neurophysiologic monitoring data. A noteworthy change was detected in 176 (70%) of the 250 patients studied. Table III lists the specific problems detected by neurophysiologic monitoring. Perfusion imbalance comprised 37% of the total number of problems detected. An abnormal pattern of cerebral perfusion was initially detected by TCD and the clinical impact of the change was assessed by cerebral oximetry or EEG, or both. Thus flow was determined to be low enough to warrant adjustment only if it was associated with depression of synaptic activity or cerebral venous oxygen desaturation. Similarly, because the TCD is exquisitely sensitive to the presence of even minute amounts of gas bubbles, notification of clinically important emboli necessitated concomitant change in cerebral oximetry or EEG, or both.

Cerebral venous oxygen desaturation was by far the most common source for intervention. Marked desaturation in excess of 20% of the precannulation baseline was the basis for 58% of the notifications. In most cases, EEG slowing eventually accompanied evidence of desaturation, although decreasing val-

ues on the oximeter nearly always preceded electrographic signs of depressed synaptic activity.

Only infrequently were signs of insufficient anesthetic depth observed. Cerebral venous oxygen desaturation, signifying an increased metabolic demand coupled with an increasing EEG mean frequency and/or loss of low-frequency delta activity, occurred in only 5% of the notifications.

Table IV lists the cases in which interventions were made in response to problems detected by neurophysiologic monitoring. The surgeon, anesthesiologist, and perfusionist were all involved in making adjustments to potential problems detected by neurophysiologic monitoring. The surgeon was directly involved in 27% of the 130 interventions made in patient management. These activities involved repositioning of the aortic or venous perfusion cannulas or a vascular clamp. Additionally, TCD-detected gas microemboli prompted further deairing measures in seven patients.

The perfusionist was involved in 52% of the adjustments. The TCD and cerebral oximeter made it clear that seemingly small changes in pump flow or perfusion pressure may have profound consequences for effective cerebral perfusion. For example, during low-flow bypass, a sudden further drop in pump flow of as little as 200 ml/min occasionally resulted in a near-cessation of cerebral perfusion

and profound desaturation, despite a drop in systemic perfusion pressure of less than 5 mm Hg.

The remaining 21% of interventions, made by the anesthesiologist, varied widely in nature from correction of airway problems to increasing anesthetic depth. Neuroprotectant doses of phenytoin and dexamethasone were administered to 10 patients in hemodynamically stable condition, when more conventional and conservative adjustments alone failed to correct the imbalance in cerebral homeostasis detected through neurophysiologic monitoring. There was no clear relationship between the failure to respond to conventional intervention and the type of surgical procedure, which included repair of atrial and ventricular septal defects, mitral valve replacements, repair of tetralogy of Fallot, and repair of pulmonary stenosis or atresia.

Postoperative outcome results. Neurologic outcome in the three groups is shown in Table VI. There was no difference in incidence of neurologic sequelae between the no-change (7%) and the intervention (6%) groups. However, the incidence in the no-intervention group (26%) was significantly ($p = 0.003$) higher. Similarly, the median length of stay in the no-intervention group was 3 days longer than in the other two groups, although this difference did not reach statistical significance because of the high variance within each group. However, the proportion of no-intervention patients discharged from the hospital within 1 week (32%) was significantly lower than that observed in either the intervention (51%, $p = 0.05$) or no-change (58%, $p = 0.01$) groups. The small sample size of phenytoin-treated patients precluded reliable determination of the drug's effect on awakening time or duration of postoperative mechanical ventilation.

Use of the three study cohorts permitted calculation of the incidence of noteworthy neurophysiologic change and the probabilities that such a change would result in a prolonged hospital stay in the presence and absence of neurophysiologic monitoring. The break-even cost was \$2142 per case, or more than four times the monitoring charges.

Discussion

During cardiopulmonary bypass, the critical balance between the delivery of oxygenated blood and the brain's metabolic demand for it is importantly influenced by a wide range of variables under the direct control of the surgical team. Historically, management of these variables has been by empir-

Table VI. Effect of neurophysiologic monitoring on neurologic complication and length of hospital stay

	No change	Intervention	No intervention
Neurocomplication	5/74 (7%)	7/130 (6%)	12/46* (26%)
Seizure	3	5	5
Cerebral infarct	1		3
Chorea	1	1	1
Visual neglect		1	
Hypotonia		1	2
Speech disorder			1
Length of stay: median (interquartile range)	6 (4-12)	6 (5-12)	9 (5-13)†
Percent discharged < 7 days	58	51	32‡

* $p = 0.003$ versus intervention; $p = 0.01$ versus no change.

†Median (interquartile range); no significant intergroup differences.

‡ $p = 0.05$ versus intervention; $p = 0.01$ versus no change.

ically derived protocol. In the absence of informative feedback from the patient's brain, individual teams rely on standard protocol for most patients. This relatively uniform approach to perfusion management may thus lead to an injurious oxygenation imbalance, particularly in the immature brains of critically ill infants with complex cardiovascular anomalies.

Neurophysiologic monitoring offers an alternative method to management of cardiopulmonary support in which each of the variables may be individualized and quickly adjusted to address changes in oxygen supply-demand balance. Because the brain has the highest blood flow and metabolic demand of any vital organ, it provides the ideal site for assessing the match between perfusion and oxygenation. The multimodality approach to neurophysiologic monitoring assures that the team has direct continuous information about the status of cerebral oxygen delivery and consumption under all circumstances, even deep hypothermic circulatory arrest.

EEG monitoring has been used successfully to detect cerebral ischemia since the earliest days of cardiac surgery.⁷ However, it has not achieved widespread acceptance by cardiac surgeons or anesthesiologists, although there is a growing concern about the neurologic and cognitive deterioration that may result from cardiopulmonary bypass. Aside from the complexity of conventional EEG analysis and its susceptibility to electrical and mechanical artifact, its value is often questioned because of poor specificity.⁸ The EEG is unquestionably very sensitive in detecting regional synaptic depression accompanying cerebral ischemia or hypoxia. Unfortunately,

many noninjurious processes may produce the same EEG changes as hypoperfusion or hypoxia.

Our approach has been to use additional monitoring modalities and an algorithm to improve specificity and consistency. The cerebral oximeter has proved invaluable because of its ability to distinguish between EEG slowing caused by ischemia versus that resulting from excessive anesthesia. In the former, inadequate oxygen delivery causes synaptic depression and cerebral venous oxygen desaturation; in the latter, anesthetic depression of synaptic function slows the EEG but increases oxygen saturation because of decreased metabolic demand. The oximeter also aids ischemia detection when the EEG is uninterpretable or absent because of artifacts, high-dose anesthesia, or deep hypothermia.

Although near-infrared spectroscopy is a promising new technology, the current commercial devices have practical and theoretical limitations. On the practical side, none have been cleared by the U.S. Food and Drug Administration for pediatric use. Therefore application of this technology requires informed parental consent sanctioned by the institutional review board. On the theoretical side, some of the devices, like the Somanetics INVOS 3100-A spectrophotometer used in the present study, measure only intravascular hemoglobin saturation. Because a number of physiologic perturbations occurring during hypothermic cardiopulmonary bypass may alter the hemoglobin dissociation curve, the oxygen saturation values do not directly indicate the amount of oxygen actually available to neurons. Some of these devices claim to measure cytochrome $a-a_3$, which may provide a direct indication of oxygenation within neuronal mitochondria. Finally, the INVOS spectrophotometer quantified the magnitude of change from a baseline established before aortic cannulation, rather than providing absolute oxygen saturation. The lack of an absolute criterion for cerebral hypoxia complicates the intervention algorithm and may lead to uncertainty.

A wide range of perfusion abnormalities can be detected promptly and unambiguously with TCD. Flow patterns can distinguish between aortic and caval obstructions, even though both may eventually produce EEG slowing or desaturation. Hyperflow velocity patterns with no accompanying EEG abnormality but a potential for intracerebral hemorrhage can be quickly detected and corrected. The hyperemia is accompanied by an elevated cerebral venous oxygen saturation.

The present study used alpha-stat acid-base man-

agement, but many centers now prefer pH-stat or a mixture of both alpha-stat and pH-stat. Because cerebral blood flow velocity is normally exquisitely sensitive to change in arterial carbon dioxide, the ultrasonic intervention criteria for hypoperfusion and hyperperfusion may have to be adjusted to reflect differing acid-base strategies.

Neuroprotection was an attempt to increase the brain's tolerance to a persistent imbalance between oxygen supply and demand. When the EEG or cerebral oximeter failed to respond to conventional measures such as increased inspired oxygen fraction or perfusion pressure, dexamethasone and phenytoin were administered to hemodynamically stable patients. Dexamethasone was used because of the membrane-stabilizing and neuroprotectant properties of corticosteroids.⁹ In contrast, phenytoin served as a sodium channel modulator to prevent accumulation of cytotoxic intracellular concentrations of sodium.¹⁰ The antiischemic and antihypoxic properties of phenytoin have been demonstrated in a wide variety of animal models,¹¹⁻¹⁶ and fosphenytoin is currently under clinical investigation in the treatment of stroke. Neuroprotectant administration has become a more attractive option with the advent of the water-soluble and cardiovascularly benign fosphenytoin.¹⁷

Results of this pilot retrospective examination of the value of neurophysiologic monitoring raise both practical and ethical questions regarding the appropriateness of subsequent prospective, randomized, controlled studies. Reduction in the neurocomplication rate was achieved by a multistage process or algorithm that depended on EEG, TCD, cerebral oximetry, and a list of appropriate corrective actions. No one device or action alone can hope to achieve comparable results. Prospective, randomized, controlled evaluation of the entire process appears to represent a daunting challenge in experimental design. The benefit of most of the corrective actions is self-evident, such as cannula adjustment or pump flow increase to improve cerebral perfusion. However, the role of neuroprotectants per se is less certain. A prospective evaluation of the actual benefit of phenytoin, dexamethasone, and other candidate neuroprotectants seems essential before their widespread adoption.

Regarding the ethical issue, TCD ultrasonography and cerebral oximetry provide direct continuous measurement of cerebral perfusion and oxygenation. A sudden precipitous coincident decline in these measures provides a clear indication of cere-

bral hypoxia and its cause. To knowingly detect this obvious deficiency and not attempt to correct the underlying problem in the name of scientific rigor appears to us to be both unethical and unconscionable. However, the informational value of some other neuromonitoring data, that is, inadequate level of anesthesia, is not as well established and could benefit from prospective randomized evaluation.

In retrospective cohort studies, the value of comparative inferential statistics is often limited by lack of true randomization and imbalance in patient assignment. This limitation applies to the current study, since as an account of our initial experience with an intervention algorithm guided by neurophysiologic monitoring it was not a truly randomized clinical trial. This inadequacy may have resulted in unintentional statistical bias, and caution is urged in interpreting the magnitude of apparent intergroup outcome differences.

Despite the potential design limitations of this study, its results suggest that the neurophysiologic monitoring algorithm can help to improve neurologic outcome in a cost-effective manner. Determination of economic benefit in many health care situations is complex, because economic benefit cannot be defined in unambiguous absolute terms. For example, the perceived cost of a postoperative neurologic complication may vary considerably, depending on the identity of the payor (i.e., insurer vs hospital vs patient) and reimbursement mechanism. Complication cost will be viewed by hospital administrators as the highest in reimbursement environments characterized by capitated payments or a poorly insured patient population. Therefore the magnitude of the favorable cost savings for neurophysiologic monitoring will undoubtedly vary widely depending on viewpoint. However, the clinical benefit of neurophysiologic monitoring—a significant reduction in neurologic sequelae—is clear and independent of the vagaries of current health care economics.

REFERENCES

1. Singer I, Edmonds HL. Changes in cerebral perfusion during third-generation implantable cardioverter-defibrillator testing. *Am Heart J* 1994;127:1052-7.
2. Edmonds HL Jr, Griffiths LK, van der Laken J, et al. Quantitative electroencephalographic monitoring during myocardial revascularization predicts postoperative disorientation and improves outcome. *J Thorac Cardiovasc Surg* 1992;103:555-563.
3. Edmonds HL Jr, Rodriguez RA, Audenaert SM, et al. The role of neuromonitoring in cardiovascular surgery. *J Cardiothorac Vasc Anesth* 1996;10:15-23.
4. Ganzel BL, Edmonds HL Jr, Pank JR. Neurophysiologic monitoring to assure delivery of retrograde cerebral perfusion. *J Thorac Cardiovasc Surg*. In press.
5. Ferry PC. Neurologic sequelae of open-heart surgery in children. *Am J Dis Child* 1990;144:369-73.
6. Rodriguez RA, Audenaert SM, Austin EH III, et al. Auditory evoked responses in children during hypothermic cardiopulmonary bypass. *Clin Neurophysiol* 1995;12:168-76.
7. Theye RA, Patrick RT, Kirklin JW. The electro-encephalogram in patients undergoing open intracardiac operations with the aid of extracorporeal circulation. *J Thorac Surg* 1957;34:709-17.
8. Witoszka MM, Tamura H, Indeglia R, et al. Electroencephalographic changes and cerebral complications in open-heart surgery. *J Thorac Cardiovasc Surg* 1973;66:855-64.
9. Bracken MD, Shepard MJ, Collins WF. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. *N Engl J Med* 1990;322:1405-11.
10. Taylor CP. Na^+ currents that fail to inactivate. *Trends Neurol Sci (TINS)* 1993;16:455-60.
11. Wohns RNW, Kerstein MD. The role of dilantin in the prevention of pulmonary edema associated with cerebral hypoxia. *Crit Care Med* 1982;10:436-43.
12. Fukuda A, Tabuse H, Ihara N, et al. Effects of phenytoin on regional cerebral blood flow, electroencephalogram and electrolyte contents in cerebral blood and cerebral cortex following total cerebral ischemia in dogs. *Circ Shock* 1983;10:341-50.
13. Hayakawa T, Hamada Y, Maihara T, et al. Phenytoin reduces neonatal hypoxic-ischemic brain damage in rats. *Life Sci* 1994;54:387-92.
14. Taft WC, Clifton GL, Blair RE, et al. Phenytoin protects against ischemia-produced neuronal cell death. *Brain Res* 1989;483:143-8.
15. Imaizumi S, Suzuki J, Kinouchi H, et al. Superior protective effects of phenytoin against hypoxia in a pharmacological screening test. *Neurol Res* 1988;10:18-24.
16. Edmonds HL Jr, Jiang YD, Zhang PY, et al. Anticonvulsant activity of topiramate and phenytoin in a rat model of ischemia-induced epilepsy. *Life Sci* 1996;59:PL127-31.
17. Ramsay RE, DeToledo J. Intravenous administration of fosphenytoin. *Neurology* 1996;46(Suppl 1):S17-19.

Discussion

Dr. Richard A. Jonas (Boston, Mass.). I congratulate Dr. Austin and Dr. Edmonds and their coauthors on another very important contribution in the area of neurophysiologic monitoring during pediatric cardiac surgery.

Many controversies exist in the management of cardiopulmonary bypass, deep hypothermia, and the use of circulatory arrest, including in particular perfusion variables, such as optimal hematocrit and optimal pH strategy. The reason for these ongoing controversies is that there is no single on-line method to confirm that oxygen delivery has been maintained to cerebral neurons throughout the brain. Surrogate end points, such as mixed venous oxygen saturation in the venous cannula and the absence of a metabolic acidosis, are highly insensitive methods for determining that brain oxygenation is adequate. In this paper, the authors have used a combination of brain monitoring modalities and have described an algorithm to determine appropriate interventions. In their

retrospective nonrandomized analysis they have found that patients who were monitored and who had interventions were less likely to have postoperative neurologic complications.

One of the main difficulties with the report, as Dr. Austin has pointed out, is the fact that patients were not randomized to an intervention versus nonintervention strategy. It would be helpful Dr. Austin, if you could further expand for us how decisions were made in the operating room as to when an intervention should be undertaken on the basis of these neurophysiologic monitoring changes. Is it possible that the method of selection in some way biased the result?

Second, I note that the near-infrared spectroscopy system that you used was the Somanetics system, which measures only cerebral oxygenation. We have had considerable experience with the Hamamatsu instrument (Hamamatsu Corp., Bridgewater, N.J.), which measures not only cerebral oxygenation but also the relative redox state of cytochrome aa3. With hemodilution, hypothermia, and with an alkaline pH strategy, such as alpha-stat, we believe that cerebral tissue oxygen status is less useful than cytochrome redox state because there may be inadequate oxygen availability despite adequate levels of hemoglobin saturation. Do you have any experience with near-infrared spectroscopy that assesses cytochrome, and how does this influence your algorithm?

Once again, I would like to congratulate the authors on an exceedingly important contribution. Both subtle and devastating neurologic injuries continue to be important problems in children undergoing heart surgery. It will only be through refinement of on-line monitoring techniques such as those described by Dr. Austin and his group that we will be able to make serious inroads into this important problem.

Dr. Austin. Thank you, Dr. Jonas. I think you clearly pointed out the difficulties with this study. As I reviewed the data and put together the presentation, I had similar concerns. Before embarking on this study I did not have many concerns about neurologic problems. As surgeons, we know that some seizures occur and that occasionally a child has a major neurologic problem. However, until I looked closely, I did not realize how significant the problem was. When Dr. Edmonds presented the oppor-

tunity to examine what goes on during cardiopulmonary bypass in patients undergoing pediatric heart surgery, I was certainly agreeable. We started this study simply to observe what happened in patients undergoing a variety of congenital heart repairs. This included some patients who had closed procedures, such as coarctation repairs and shunts. I must say that I was impressed with the number of abnormalities that we detected. Of course, at the beginning we did not really know how to respond. As I indicated in my presentation, there were some cases in which I just believed we had to respond. If when you start bypass the cerebral flow drops, the EEG changes, and there is a significant drop in oximetry, you feel obliged to do something. Clearly in those cases that I mentioned, something was done. On the other hand, there are more subtle situations such as when you are rewarming from bypass and the oximetry drops. Usually everything else seems to be acceptable, and if you were not monitoring, you would not do anything. Early in our experience we did not do anything, and, quite honestly, it is hard to determine at what particular point we decided to change. Much of what was done was not even decided by the surgeon; it was decided by the anesthesiologist working with the perfusionist deciding whether to increase pump flow or increase the arterial pressure with a vasoconstrictor. Usually when those changes were made, the oximetry would return toward baseline. I recognize that our approach to intervention may have introduced some bias with this study, and I think it warrants proceeding with further studies done in a more randomized fashion to verify our findings. However, we would have to select certain patients for the randomized approach, because I would find it unethical not to intervene in those cases in which there was a clear-cut change associated with a clear-cut change in the EEG.

We have no experience with the device that you are using, which indicates cytochrome redox state. I am dependent on what Dr. Edmonds, my associate, provides, and we have not applied the device that you have mentioned. All of this experience was derived with the use of the Somanetics system.

For appendix see next page.

Appendix

Neuromonitoring break-even analysis*

Model parameters:

P_1 = Probability of complication in monitored patient

P_2 = Unmonitored

C_1 = Monitoring cost/case

C_2 = Intensive care unit complication cost/day

V = Annual case volume

X = Cost of uncontrollable complication (i.e., no monitored changes)

Monitoring scenario cost:

$$M = C_1V + X + P_1 (6C_2)V \text{ with } P_1 = (7/130)(176/250) = 0.038$$

$$M = X + V (C_1 + 0.038[6C_2])$$

$$M = X + V (C_1 + 0.228 C_2)$$

Unmonitored scenario cost:

$$U = X + P_2(9C_2) V \text{ with } P_2 = (12/46)(176/250) = 0.184$$

$$U = X + V (0.184 [9C_2])$$

$$U = X + V (1.656 C_2)$$

Break-even point:

$$M = U$$

$$X + V (C_1 + 0.228 C_2) = X + V (1.656 C_2)$$

$$V (C_1 + 0.228 C_2) = V (1.656 C_2) \text{ with } V > 0, C_1 + 0.228 C_2 = 1.656 C_2$$

$$C_1 + 1.428 C_2 \text{ at } C_2 = \$1500, C_1 = \$2142$$

*Reinhardt UE. Break-even analysis for Lockheed's Tri-Star: an application of financial theory. J Finance 1973;28:821-8.