QUANTITATIVE ELECTROENCEPHALOGRAPHY: A METHOD TO ASSESS CEREBRAL INJURY AFTER HYPOTHERMIC CIRCULATORY ARREST

Although hypothermic circulatory arrest and low-flow cardiopulmonary bypass are routinely used for surgical correction of congenital cardiac anomalies, use of long durations of arrest, often required for more complex repairs, raises serious concerns about cerebral safety. Searching for an intraoperative assessment that can reliably predict cerebral injury, we have found an excellent correlation between changes in quantitative electroencephalography intraoperatively and immediately postoperatively after prolonged hypothermic arrest, and neurologic and behavioral evidence of cerebral injury. After epidural placement of four recording electroencephalographic electrodes and baseline neurologic/behavioral and electroencephalographic assessment, 32 puppies were randomly assigned to one of four groups: hypothermic controls in which cooling to 18° C was followed immediately by rewarming, 30 minutes of hypothermic circulatory arrest at 18° C, 90 minutes of arrest at 18° C, and 90 minutes of low-flow cardiopulmonary bypass at 25 ml/kg per minute at 18° C. An electroencephalogram was recorded at baseline, after cooling, during rewarming, and at 2, 4, and 8 hours after the start of rewarming, as well as before the operation and 1 week after the operation. Postoperative neurologic and behavioral outcome was assessed 24 hours after cardiopulmonary bypass and daily for 1 week by means of a graded scale in which 0 is normal and 12 and 13 indicate severe neurologic injury (coma and death). Thirty animals survived the experimental protocol: two animals in the 90-minute hypothermic arrest group died before neurologic evaluation could be completed, and the remainder exhibited various degrees of neurologic and behavioral impairment, more severe on day 1 than on day 6. No animal in the remaining groups had a significant neurologic deficit. Quantitative electroencephalographic analysis shows marked differences between the 90-minute arrest group and the controls in the percent electroencephalographic silence during rewarming and at 2 hours, and in the percent recovery of baseline power at 2, 4, and 8 hours. At 2 hours after the start of rewarming, a correlation between electroencephalographic amplitude and neurologic/behavioral score on day 1 was carried out, which predicts with great certainty ($p < 0.00001$) that if electroencephalographic power at this time is less than $500 \mu V^2$, overt neurologic injury will subsequently become apparent. In addition, a significant shift from higher to lower frequency in the day 6 postoperative electroencephalogram compared with baseline occurs only in the 90-minute arrest group. Although clinical neurologic injury was not apparent in any but the 90-minute arrest group, further quantitative electroencephalographic com-

Craig K. Mezrow, MS^a (by invitation), Peter S. Midulla, MD^a (by invitation), Ali M. Sadeghi, MD^a (by invitation), Alejandro Gandsas, MD^a (by invitation), Weijia Wang, MD^b (by invitation), Howard H. Shiang, DVM^a (by invitation), Carol Bodian, PhD^c (by invitation), Otto E. Dapunt, MD^a (by invitation), Rosario Zappulla, MD, PhD^b (by invitation), and Randall B. Griepp, MD, New York, N.Y.

From the Departments of Cardiothoracic Surgery,^a Neurosurgery,^b and Biomathematical Sciences,^c Mount Sinai Medical Center, New York, N.Y.

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Address for reprints: Craig Mezrow, MS, Department of Cardiothoracic Surgery, Mount Sinai Medical Center, P.O. Box 1028, New York, NY 10029.

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parisons of postoperative with baseline power show a much more rapid return of electroencephalographic power in the control than in either the 30-minute hypothermic arrest or the low-flow cardiopulmonary bypass group. Between-group comparisons show significant differences between the 90-minute arrest and low-flow cardiopulmonary bypass groups at several time points, and fewer and less marked differences between 90-minute and 30-minute arrest groups. These results demonstrate that quantitative electroencephalographic logic injury after 90 minutes of hypothermic circulatory arrest at 18° C. The presence of milder but significant differences from control quantitative electroencephalographic values after 30 minutes of arrest at 18° C suggest that there may be subtle cerebral injury undetected by neurologic/behavioral evaluation in this group, although this interval is clinically accepted as safe. In contrast, no quantitative electroencephalographic evidence of cerebral dysfunction was apparent after 90 minutes of low-flow cardiopulmonary bypass at 18° C. The study as a whole suggests that quantitative electroencephalographic is a sensitive indicator of cerebral injury and may prove extremely valuable in future studies of strategies for cerebral protection during cardiac surgery. (J THORAC CARDIOVASC SURG 1995;109:925-34)

In recent years there has been increasing concern about the possible deleterious effects of neonatal cardiac surgery on later intellectual function, especially when prolonged durations of hypothermic circulatory arrest (HCA) are used. Because of the complexity of assessing what may be relatively subtle cerebral injury in a heterogeneous population years away from manifesting the consequences of a neurologic insult, as well as the many other obstacles in the way of a definitive study of the cerebral consequences of neonatal cardiac surgery in children, we embarked on a systematic exploration of some aspects of this problem in weanling puppies.

One of our aims has been to try to identify intraoperative parameters that will correlate with later evidence of cerebral injury, as determined by neurologic and behavioral evaluation of long-term survivors: this is an essential step toward analyzing the cause of cerebral injury after HCA. Identification of such factors will also prove invaluable for devising and screening strategies to improve cerebral protection during neonatal cardiac surgery, with the ultimate goal of preventing cerebral injury after HCA.

In the course of our studies, we have begun to record quantitative electroencephalography (QEEG) before and after our acute hypothermia protocol, as well as during the operation. We also evaluate cerebral blood flow, cerebral vascular resistance, and cerebral metabolism during and after HCA under a variety of circumstances. During a study in which no overt neurologic damage was evident after HCA for 60 minutes

at 18° C, we found a postoperative shift of EEG waveforms to slower frequencies, a finding that correlates with cerebral injury in a number of other contexts.¹

In the current study, we extended the interval of HCA at 18° C to 90 minutes, anticipating that we would find both clinical and further EEG evidence of cerebral injury. We report the results of intraoperative QEEG, as well as preoperative and postoperative telemetric QEEG studies, in 32 puppies divided into four groups: a hypothermic control, in which puppies were cooled to 18° C and immediately rewarmed; a group subjected to 30 minutes of HCA at 18° C; a group that underwent HCA at 18° C for 90 minutes, and a group subjected to low-flow cardiopulmonary bypass (CPB) at 18° C for 90 minutes. The metabolic results from this experiment are found in the accompanying paper (see page 959).

Our data show clinical evidence of cerebral injury only in the group subjected to 90 minutes of HCA at 18° C. The clinical findings in the 90-minute HCA group were accompanied by significant differences from the other groups in intraoperative and postoperative QEEG findings, suggesting that QEEG is a sensitive and reliable indicator of cerebral injury. The presence of milder but still statistically significant QEEG changes of a similar character in the 30-minute HCA group, as well as some differences from control patterns even in the LFCPB group suggest that QEEG may also be a way of detecting subclinical cerebral injury.

Materials and methods

Thirty-two weanling beagles (Marshall Farms, North Rose, N.Y.), 3 months of age, weighing 3.5 to 5 kg, were randomly assigned to one of four groups after CPB cooling:

1. Control group: immediate rewarming after cooling to 18° C
2. Thirty-minute HCA at 18° C
3. Ninety-minute HCA at 18° C
4. Ninety-minute low-flow cardiopulmonary bypass at 18° C

Each animal underwent epidural electrode placement, preoperative EEG monitoring, and neurologic/behavioral assessment, intraoperative EEG monitoring, and postoperative EEG and neurologic behavioral examinations.

Perioperative management. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). The protocol for these experiments was approved by the Mount Sinai Institutional Animal Care and Use Committee.

Epidural electrode implantation. After anesthesia with ketamine (20 mg/kg) and diazepam (Valium, 1 mg/kg), animals were intubated and supported by positive-pressure ventilation with halothane anesthesia. A midline scalp incision was made and the underlying periosteum removed to facilitate identification of the coronal and sagittal sutures. Four recording electrodes (left and right frontal and parietal) were positioned epidurally and cemented (Durelon cement, ESPE-Premier, Norristown, Pa.) in 2 mm burr drilled holes. The frontal electrodes were implanted 1.5 cm to the left and to the right of the sagittal suture directly behind the coronal suture, and the parietal electrode was placed 1.5 cm caudal to the frontal electrode on each side. The leads from the electrodes were passed subcutaneously, externalized, and sutured to the dorsum of the neck.

Neurologic and behavioral evaluation. Puppies were examined before the operation for evaluation of behavioral and/or neurologic deficits; although they are reported only for postoperative days 1 and 6, these assessments were repeated daily after the operation. Each animal was evaluated and scored for abnormalities by a veterinarian unaware of the experimental design. The scores ranged from 0 if no abnormalities were noted to 12 if the animal was comatose and 13 if dead. The following parameters were evaluated:

Behavioral exam

Mental status

- Depressed
- Stuporous
- Comatose

Gait

- Unsteady
- Unable to walk
- Unable to stand

Appetite

- Decreased
- Refuses solids
- Refuses liquids

Affect

- Aggressive
- Indifferent
- Bizarre

Neurologic exam

Posture

- Wheelbarrowing reaction
- Hopping reaction
- Extensor postural thrust reaction
- Placing reaction

Reflexes

- Right and left quadriceps
- Right and left extensor carpi radialis

Cranial nerves

- Menace reaction
- Licking reaction
- Olfactory reaction
- Pupillary reflex

Telemetric EEG recording. After the animals had recovered from the epidural implantation procedure, two 10-minute recordings of "awake" EEG were acquired in a darkened room before the operation. This was accomplished via telemetry (Telefactor Corp., West Conshohocken, Pa.) and transmitted to a Spectrum 32 monitor (Cadwell Laboratories, Kennewick, Wash.), where it was further amplified, filtered, digitized, and stored for subsequent analysis. On postoperative day 6, awake EEG recordings were again undertaken in the same way as described for the preoperative recordings.

Intraoperative protocol and monitoring

Anesthesia. Animals were pretreated with glycopyrrolate (0.025 mg/kg), anesthetized with fentanyl (25 to 50 µg/kg per hour) and isoflurane (<1%), and intubated. They were supported by positive-pressure ventilation (inspired oxygen fraction > 40%; arterial carbon dioxide tension 35 to 40 mm Hg) and paralyzed with pancuronium (0.1 mg/kg). Arterial oxygen tension was maintained above 100 mm Hg. Lead II was used for electrocardiographic (ECG) monitoring. Esophageal, rectal, and epidural temperature probes were placed and peripheral vessel cannulations were performed for monitoring purposes.

CPB, cooling, and rewarming. After heparinization (300 IU/kg), nonpulsatile CPB was instituted with a single cannula in the right atrium with return of the arterial perfusate via the ascending aorta. Membrane oxygenators (VPCML plus, Cobe Laboratories, Inc., Lakewood, Colo.) were primed with a hemodilute solution containing homologous blood (universal donor), 5% albumin, furosemide (1 mg/kg), heparin (2000 IU), 1% dextrose in 0.9% saline solution, and potassium chloride (1 mEq/kg).

CPB was established at a rate of 100 ml/kg per minute, and hematocrit value was maintained between 22% and 28%. Surface cooling was begun with a cooling blanket. In accordance with the principles of alpha-stat management, pH during cooling was maintained at 7.4 ± 0.05 and arterial carbon dioxide tension at 35 to 40 mm Hg,

uncorrected for temperature. CPB flow was reduced to 50 ml/kg per minute at an esophageal temperature of 20° C and cooling was then continued to an esophageal temperature of 18° C.

Control animals were immediately rewarmed after cooling to 18° C. Circulatory arrest was established in animals assigned to HCA, and the perfusate was drained into the oxygenator reservoir. Animals assigned to LFCPB were perfused for 90 minutes at a CPB flow rate of 25 ml/kg per minute. In contrast to all previous studies from this laboratory, in none of the animals in this study was the head packed in ice.

All animals were perfusion/surface rewarmed (CPB at 75 to 100 ml/kg per minute for 35 to 45 minutes) to an esophageal temperature of more than 36° C and the animals were then weaned from CPB. After decannulation, protamine sulfate (5 mg/kg) was administered to reverse heparinization.

Arterial blood pH, oxygen tension, carbon dioxide tension, hematocrit, and oxygen content were measured with a model 288 Ciba Corning Diagnostics Corp. analyzer (Medfield, Mass.).

Further detail concerning cooling and rewarming, arterial pH, and blood pressure can be found in the accompanying manuscript.

Intraoperative EEG—acquisition and analysis. Three-minute sessions of EEG were acquired and stored for subsequent analysis at six time points during the experiments:

1. Baseline: at 37° C before CPB
2. After cooling to 18° C
3. During rewarming at 30° C (approximately 15 minutes after the institution of rewarming)
4. Two hours after the start of rewarming (after termination of CPB, at 37° C, with closed thorax)
5. Four hours after the start of rewarming
6. Eight hours after the start of rewarming

These intraoperative time points correspond to the times at which metabolic measurements of cerebral blood flow and vascular resistance, and oxygen uptake and metabolism were also determined, as detailed in the accompanying manuscript.

Spectral analysis was performed on 50 seconds of artifact-free EEG for each of the recording electrodes. The QEEG values for the frontal electrodes were averaged and analyzed separately from the parietal electrodes for each time point.

Intraoperative QEEG findings at 2, 4, and 8 hours after the start of rewarming were compared with those at baseline and also between different groups. EEG power was calculated as twenty distinct bands (1 to 20 Hz) and compared either with baseline recordings or with recordings from the other experimental groups at the same time point, as indicated in the results. In the graph of QEEG power at the 2-hour time point, the two frontal and two parietal electrodes were averaged for each experimental group to generate a single line showing the value of the QEEG at each frequency.

The same comparisons were not carried out for the earlier time points (at the end of cooling and during rewarming) because the EEG is not continuous at those

times: irregular intervals of burst suppression make this type of analysis impossible. EEG was therefore analyzed as percent silence after cooling, during rewarming, and early in the postoperative period.

Preoperative and postoperative EEG analysis. Spectral analysis was performed on 50 seconds of artifact-free EEG for each of the recording electrodes. The EEG power was calculated as four distinct bands: delta (0.5 to 3.0 Hz), theta (3.0 to 8.0 Hz), alpha (8.0 to 13 Hz), and beta (13 to 20 Hz). The QEEG results of the frontal electrodes were averaged and analyzed separately from those of the parietal electrodes, and analyses were carried out on the basis of changes in the spectral bands after the operation versus before.

The change in the predominant frequency of the postoperative versus the preoperative EEG was looked at in various ways to see whether a shift to lower frequency—a finding generally agreed on to correlate with cerebral injury²⁻⁴—had occurred in any of the groups. The most discriminating calculation of frequency shift is the change in the amount of theta (postoperative – preoperative) subtracted from the change in delta (postoperative – preoperative).

Statistical methods. Statistical analysis of the EEG data was conducted separately for the averages of the two frontal leads and for the corresponding averages of the two parietal leads. With few exceptions, the results were the same. Results of both are given when they did not substantially agree. For ease of presentation, some of the graphs show results for the averages of all four leads.

Differences in EEG power among the four experimental groups were analyzed in two steps. First, for each frequency band, a one-way Kruskal-Wallis analysis of variance was performed to test whether there were any differences among the four experimental groups, with a *p* value of 0.05 or less considered statistically significant. Then, for those bands with a significant result, each of the six possible pairs of groups was compared. The significance level of these pairwise comparisons was adjusted by means of the Bonferroni correction to preserve a 5% significance level for the set of six tests. This means that some comparisons that would have been significant at the 5% level on the basis of conducting a single test did not meet the more stringent criterion. For pairs in which this happened repeatedly and in a consistent fashion, the results are described as suggestive of significant differences, with the idea that the statistical results might have been more convincing had we had the luxury of studying a greater number of animals.

Within-group comparisons of changes in EEG power from baseline at 2, 4, and 8 hours after the operation were analyzed by Wilcoxon signed rank tests, with a Bonferroni correction to preserve a 5% significance level for each set of three comparisons.

The correlation of postoperative neurologic and behavioral results with the QEEG amplitude at 2 hours was the first statistical test performed. Some of the more subtle distinctions suggested by this initial analysis could not be confirmed by the more stringent techniques subsequently used and reported herein.

Results

Morbidity, mortality, and neurologic outcome.

Of the 32 puppies in the experimental group, only two died, both after 90 minutes of HCA. In one, there was clearly neurologic damage, and in the other, multiorgan failure resulted in death before the possibility of full neurologic evaluation. Because both animals survived the acute experimental protocol, their QEEG data were included in the calculation of intraoperative parameters, and their neurologic outcome was scored at the highest possible level throughout the follow-up period, although formal neurologic/behavioral evaluation could not be carried out.

Of the surviving animals, only those in the 90-minute HCA group had clinically evident neurologic or behavioral impairment at the time of initial postoperative evaluation. Most of the animals in the 90-minute HCA group had poor appetite, indifferent affect, and were unable to walk or even stand on the first postoperative day; their average behavioral score was 5.5 ± 0.6 ; average neurologic score was 10.3 ± 0.7 . By day 6, however, most of the puppies had improved considerably, with only minor residual gait abnormalities and a few abnormal reflexes. After 6 days, average behavioral and neurologic scores were 0.8 ± 0.3 and 4.3 ± 1.1 for the surviving animals in the 90-minute HCA group. In contrast to the universal evidence of at least transient cerebral injury in the 90-minute HCA group, none of the animals in any of the three other groups had serious neurologic or behavioral sequelae, as documented in Table I of the accompanying paper.

Intraoperative EEG. Because the EEG is not continuous prior to the 2-hour time point, QEEG results at the end of cooling, during rewarming, and at 2 hours after the operation were analyzed in terms of the amount of residual or returning EEG activity (Fig. 1), expressed as the percent EEG silence.

There were no significant differences among the groups in the percent EEG silence at the end of cooling, but both the 30-minute and the 90-minute HCA groups showed significant differences from both control and LFCPB groups during rewarming, with much higher levels of EEG activity in the two latter groups. Differences between the 90-minute HCA group were more highly significant ($p < 0.01$) versus control than versus LFCPB ($p < 0.05$). At the 2-hour time point, the 30-minute HCA group was no longer significantly different from the control or LFCPB groups, but the 90-minute HCA group still

Fig. 1. Percent EEG silence for the four experimental groups: at the end of cooling, at 30° C (during rewarming), and at 2 hours after the start of rewarming. As EEG is discontinuous at these time points, groups are compared based on the basis of the percent of EEG silence. A higher percent silence is equivalent to lower EEG power with continuous EEG data.

had a greater degree of EEG suppression than any other group.

Intraoperative EEG power was assessed beginning at 2 hours after the start of rewarming and also at 4 and 8 hours after the operation. Fig. 2 shows the average power 2 hours after the start of rewarming for each experimental group at each frequency as a percent of the baseline value. The graph, in which the average values for all four electrodes have been combined, shows how closely intertwined the control and LFCPB values are, and that these groups show a greater degree of recovery from hypothermia at this time than either the 30-minute or the 90-minute HCA groups.

Fig. 3 shows a more quantitative comparison of the recovery of EEG power after hypothermia at 2, 4 and 8 hours after the start of rewarming. It shows the number of frequency bands with significant differences from baseline power at each of these postoperative time points. In the 90-minute HCA group, there is a significant differences from baseline power at each of these postoperative time points. In the 90-minute HCA group, there is a significant difference from baseline levels of power in all frequency bands lasting as long as 8 hours after the operation. By 8 hours after 30 minutes of HCA, however, power is significantly lower than baseline values in only half the frequency bands. Similarly, the findings in the LFCPB group show a return to

Fig. 2. Percent of baseline quantitative EEG 2 hours after the start of rewarming. The graph depicts the average power for each experimental group for each of the 20 frequency bands (1 to 20). The LFCPB and control groups are closely intertwined and show a greater degree of EEG recovery than either of the HCA groups at every frequency band.

Fig. 3. Number of frequency bands significantly different from baseline at 2, 4, and 8 hours after rewarming. This is a more quantitative comparison of the recovery of EEG power: the more bands significantly different from baseline, the worse the recovery of EEG power.

baseline values in half the frequency bands by 8 hours after LFCPB. In contrast, the hypothermic control group shows a return to baseline values of more than half the frequency bands already at the 2-hour time point and no difference from baseline values by 8 hours after hypothermia.

The number of frequency bands in the intraoperative QEEG at 2 hours after the start of rewarming that show significant differences between the different experimental groups are shown graphically in Fig. 4. There is a highly significant difference in EEG power between the 90-minute HCA group and the control group and between the 90-minute HCA group and the LFCPB group at this time point. EEG

Fig. 4. Intraoperative QEEG differences between the groups at the 2-hour measurement. This intergroup comparison demonstrates the number of frequency bands that are significantly different between the groups. There are a far greater number of bands that are significantly different between the 90 min HCA group and both control and LFCPB groups than between 90 min HCA and 30 min HCA groups. The 30 min HCA group is also significantly different from both the control and the LFCPB groups, but not for as many bands.

power in the 30-minute HCA group is also significantly different from both the control and the LFCPB groups, but not for as many frequency bands. These results echo the findings from the percent EEG silence analysis at the same time point, which also shows differences between each of the HCA groups and the control and LFCPB groups.

Quantitative comparisons of the differences between groups in percent baseline QEEG power 4 hours after the start of rewarming are shown graph-

Fig. 5. Intraoperative QEEG differences between groups at the 4-hour measurement. As in Fig. 4, there remains a large difference between the 90 min HCA and control and LFCPB groups and a smaller difference between 90 min HCA and 30 min HCA groups. There remains a difference between 30 min HCA and control groups.

Fig. 6. Intraoperative QEEG differences between groups at the 8-hour measurement. At 8 hours there is a clear difference in EEG power between the 90 min HCA group and all others. By this late time point, there are no differences between the 30 min HCA or the LFCPB and the control groups.

ically in Fig. 5. Again a highly significant difference between the 90-minute HCA and control groups and between the 90-minute HCA and LFCPB groups is evident in most frequency bands, and there is a suggestion in some frequency bands that a significant difference is also present between the results from the 90-minute HCA and the 30-minute HCA groups. There is again a difference in some frequency bands between the 30-minute HCA group and the controls.

At the 8-hour time point (Fig. 6), the results of comparisons between groups show a clear differentiation between the 90-minute HCA group and all the others, which corresponds to the results of clinical neurologic/behavioral evaluation. There is a significant difference between the 90-minute HCA group and the control group in most frequency bands and a significant difference between the 90-minute HCA and both the LFCPB and the 30-minute HCA groups in about a third of the frequency bands. Neither the 30-minute HCA nor the LFCPB group shows any significant differences from one another or from the control at this late time point.

The QEEG data from the 2-hour time point show a highly significant correlation with the neurologic/behavioral score, as shown in Fig. 7. This validates the notion that the rate of recovery of EEG power during the operation can be useful in anticipating cerebral injury. In fact, the graph of this correlation indicates that an amplitude below $500 \mu V^2$ 2 hours after the start of rewarming predicts development of clinically evident neurologic impairment.

In summary, the return to baseline power in the four groups shows interesting differences, with the expected early return of the control group, and the markedly prolonged depression of QEEG in the 90-minute HCA group. Although the graphs of the intraoperative data appear to show very little difference between the 30-minute HCA and the LFCPB groups, the intergroup comparisons show greater differences from the control pattern of recovery in the 30-minute HCA group than in the LFCPB group and fewer differences from the 90-minute HCA group. The more prolonged EEG silence and the less rapid recovery of EEG power in the 30-minute HCA group as compared with the LFCPB group suggest that the 30-minute HCA group may have had a greater cerebral insult than the LFCPB group. The fact that there are significant differences in the data at some time points between the 30-minute HCA group and the 90-minute HCA group is compatible with the idea that the cerebral insult to the 30-minute HCA group is considerably milder than the insult that follows the longer interval of HCA; clearly it is not severe enough to be manifested clinically in the neurologic/behavioral score.

Extending this logic, the failure to find significant differences between the pattern of recovery of the EEG between control and LFCPB groups is predictive of the absence of clinically apparent impairment in the LFCPB group which was observed, and suggests even milder subclinical cerebral injury after 90 minutes of LFCPB than after 30 minutes of HCA.

Fig. 7. Neurologic/behavioral score versus EEG power at the 2-hour measurement. EEG power of less than $500 \mu V^2$ at this time point was associated with later overt neurologic impairment.

Fig. 8. Changes in relative EEG power (percent of shift to lower frequencies): preoperative versus postoperative values. Significant differences were found in the parietal leads between the 90 min HCA group and both the control group and the LFCPB group. Differences in the frontal leads were not statistically significant.

Preoperative versus postoperative QEEG results. Preoperative evaluation of relative power showed the EEG of all groups to be comparable. Postoperatively, marginal differences from preoperative values, not significant when the stringent criteria for multiple testing were applied, were seen only in the 90-minute HCA group. These differences were in the relative power in the beta and theta frequencies.

Frequency shifts, particularly from higher to lower frequencies, have been identified as a powerful prognosticator in a number of contexts in which brain injury may occur.²⁻⁴ In comparing the relative amounts of delta and theta activity before and after operation, there is a significant difference between the magnitude of these shifts in the parietal leads of

the 90-minute HCA group compared with the control and also the LFCPB groups (Fig. 8); although the frontal leads show a similar trend, it is not statistically significant. A difference of marginal significance is present between 90-minute HCA and 30-minute HCA groups.

There were no significant differences in any of these parameters between the LFCPB and the control groups or between the 30-minute HCA group and either of the other groups in which no clinically apparent neurologic/behavioral deficits were present. The presence of differences in these prognostically important postoperative EEG results between the group in which clinically evident cerebral injury was present and the groups in which clinical injury was not apparent should be noted.

A summary of the differences in both clinical and QEEG data among the four experimental groups is presented in Table I.

Metabolic data. The metabolic data from all the intraoperative time points are presented in the accompanying report. Although many measurements after hypothermia were significantly different from control values, and often varied significantly from one group to another at the same time point, the trends were similar, although all the metabolic changes were most marked in the 90-minute HCA group. The data showed a hyperemia after rewarming only in the HCA groups, followed by a rise in cerebral vascular resistance and a fall in cerebral blood flow in all groups at 2 and 4 hours after the start of rewarming, with an increase in oxygen and glucose extraction allowing a prompt return to baseline levels of cerebral metabolism.

Table I. QEEG summary

	Percent EEG silence		Frequency fractionated power			Low-frequency EEG shift	Neurologic behavioral evaluation
	30° C	2 hr	2 hr	4 hr	8 hr		
Control vs 90 min LFCPB							
Control vs 30 min HCA	X		X	X			
Control vs 90 min HCA	X	X	X	X	X	X	X
30 min HCA vs 90 min LFCPB	X						
90 min HCA vs 90 min LFCPB	X	X	X	X	X	X	X
90 min HCA vs 30 min HCA					X		X

X indicates presence of significant differences between the groups.

Discussion

The results of this study, in which intraoperative and postoperative QEEG suppression and power data and late postoperative QEEG frequency shifts all correlate with the occurrence of overt neurologic injury in puppies subjected to 90 minutes of HCA at 18° C, are convincing evidence that QEEG is a sensitive and reliable tool for the detection of cerebral injury after HCA. The significant differences present in comparisons of the 30-minute HCA group with hypothermic controls, in neither of which clinical evidence of cerebral injury was present, suggest that QEEG may detect subtle subclinical neurologic injury as well as more severe cerebral damage.

A number of investigators have urged the routine use of intraoperative EEG monitoring during cardiac surgical procedures as a means of detecting potentially dangerous situations in time to make modifications and avert neurologic injury.⁵⁻⁷ This study suggests that intraoperative QEEG is indeed a useful prognosticator of later cerebral injury and that it has potential clinical utility during procedures involving HCA both intraoperatively and in the immediate postoperative period.

The study also suggests that QEEG may be a sensitive tool for the detection of cerebral injury in future experimental studies in which interventions designed to improve cerebral protection are screened. The recognition that specific QEEG changes correlate well with clinical evidence of cerebral injury and that QEEG may detect even subclinical cerebral insults will greatly simplify the evaluation of pharmacologic and other strategies designed to prevent neurologic damage during cardiac surgery in infants with congenital heart disease.

The presence of postoperative shifts in QEEG to slower frequencies in the puppies after 90 minutes of HCA at 18° C, a type of EEG change acknowl-

edged to augur a poor prognosis,²⁻⁴ correlates with the presence of at least transient clinical cerebral injury in the puppies in this group and suggests that HCA should not be carried out for such a long interval at this temperature. As discussed in greater detail in the accompanying manuscript, cooling to a lower temperature before the start of HCA would likely confer greater protection because it would reduce the level of residual cerebral metabolism during the interval of circulatory arrest. The presence of bursts of EEG activity at 18° C in all groups in this study reinforces the notion that the brain is not completely quiescent at 18° C.

The presence of some differences between EEG power intraoperatively in the group undergoing 30 minutes of HCA at 18° C and the control group, despite the absence of clinically evident cerebral injury in this group, suggests that even shorter intervals of HCA at 18° C may not be entirely benign. Again, cooling to a lower temperature before the onset of HCA would theoretically improve cerebral protection during short as well as more prolonged intervals of HCA.

The absence of significant differences between LFCPB QEEG data and that of the controls suggests that LFCPB is less worrisome than even short periods of HCA in terms of its potential for cerebral injury. The lack of late QEEG evidence of cerebral injury in the LFCPB group in this study is in contrast to our previous study, in which statistically significant differences between preoperative and late postoperative QEEG were present not only in the 60-minute HCA group but also in the 60-minute LFCPB group, but not in two groups undergoing HCA at colder temperatures. Subsequent analysis of our earlier data by means of the more stringent techniques used in this study fail to confirm that the differences between the groups in the earlier study are truly significant.

We are disappointed by the difficulty in obtaining clear-cut and consistent differences in late QEEG findings: we attribute this difficulty to the greater variability of awake telemetric EEG recordings when compared with intraoperative EEG data and to the very small number of animals in each group in both studies. We recognize that we are in the early stages of exploring the use of QEEG to detect cerebral injury associated with hypothermia: the absence of clear-cut reproducible changes in the late postoperative recordings suggests that intraoperative and immediate postoperative QEEG may be more sensitive and reliable than later QEEG measurements in our experimental model. The more abundant evidence of clinical neurologic injury on postoperative day 1 compared with day 6 in the 90-minute HCA group parallels the seemingly greater sensitivity of QEEG in detecting cerebral injury at earlier time points.

The presence of some differences from control patterns of recovery of EEG power in the 90-minute LFCPB group and the presence of worrisome metabolic changes similar to those in the 90-minute HCA group (as described in the accompanying manuscript) leave open the possibility that colder temperatures for LFCPB as well as for HCA might improve results. The recognition that even LFCPB may not be entirely free of the potential for undesirable cerebral sequelae provides added impetus for continuing to explore ways in which cerebral protection during cardiac surgery could be enhanced. We believe strongly that QEEG will prove a valuable tool in this endeavor.

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Discussion

Dr. Julie A. Swain (*Las Vegas, Nev.*). The methods that you used are important to find a screening method that does not require survival studies, both for the manpower required to carry out a survival study, as well as for animal comfort and the political aspects of postoperative recovery studies.

What was your pH method in these animals? You had a scatter plot of the 90-minute HCA group which showed that one animal did very poorly and some of them did much better. Have you analyzed what possible differences there were in the animals that did relatively better after 90 minutes of HCA?

Dr. Mezrow. We used alpha-stat blood gas management during the conduct of the study. With regard to the degree of cerebral injury of the surviving animals after 90 minutes of HCA, because of the small number of animals per group we have no explanation why the outcome of some animals was better than others. It is of interest that the two animals that died after 90 minutes of HCA had high cerebral vascular resistance and oxygen extraction before bypass in comparison with the other animals. This may have predisposed the animals to increased risk for cerebral injury when subjected to 90 minutes of HCA.

Dr. Ralph D. Siewers (*Pittsburgh, Pa.*). What anesthesia were you using in these animals?

Dr. Mezrow. The anesthetic regimen consisted of fentanyl supplemented with isoflurane (<1%).

Dr. Siewers. You anticipate that that did not affect EEG function?

Dr. Mezrow. Anesthetic-induced EEG changes cannot be avoided. We minimized anesthetic-related differences between animal groups by administering a continuous infusion of the same dose of fentanyl per kilogram supplemented with isoflurane in each animal.

Dr. Siewers. I wondered about the implication for interpretation of intraoperative EEGs, quantitative monitoring of EEGs interoperatively, and how much that would depend on various anesthetic techniques.