Relation of Seizures After Cardiac Surgery in Early Infancy to Neurodevelopmental Outcome

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Background—The outcome of infants who have transient seizures after open heart surgery has not been studied. Using the database of the Boston Circulatory Arrest Study involving 171 children with D-transposition of the great arteries, we explored the relationship between early postoperative clinical and EEG seizures and neurodevelopmental outcomes at ages 1 and 2½ years.

Methods and Results—At 1 year, children returned for developmental and neurological evaluations and MRI. Parent-completed developmental questionnaires were collected at 2½ years of age. At 1 year, children with early postoperative seizures had lower Psychomotor Development Index (motor function) scores (clinical seizures: 12.9 mean difference [MD]; 95% confidence interval [CI], 2.2 to 23.6; P=.02; EEG seizures: 13.3 MD; 95% CI, 6.8 to 19.7; P<.001). Mental Developmental Index scores of children with clinical or EEG seizures were also lower, but the differences were not statistically significant. Infants with seizures were more likely to have an abnormal neurological examination (clinical seizures: 78% versus 31%; P=.008; EEG seizures: 58% versus 34%; P=.04). Children with EEG seizures were more likely to have MRI abnormalities (43% versus 13%, P=.002). At age 2½, children with EEG seizures had lower scores in several areas of function.

Conclusions—In infants undergoing the arterial switch operation for correction of D-transposition of the great arteries, transient postoperative clinical and EEG seizures were associated with worse neurodevelopmental outcomes at ages 1 and 2½ years as well as neurological and MRI abnormalities at 1 year of age. The occurrence of such seizures may provide an early sign of brain injury with neurological and developmental sequelae. (Circulation. 1998;97:773-779.)

Key Words: surgery ■ seizures ■ circulation ■ child development

In 1988, we began a randomized clinical trial to compare neurodevelopmental outcomes in children with D-TGA with IVS or with VSD undergoing the arterial switch operation whom we assigned to a strategy consisting predominantly of total circulatory arrest or of low-flow cardiopulmonary bypass. Among the combined treatment groups, 6% of infants had clinical seizures in the first postoperative week, and 20% had ictal activity on continuous video EEG monitoring during the first 48 postoperative hours, although no child continued to have seizures after hospital discharge or required long-term anticonvulsant therapy. Independent risk factors for both postoperative clinical and EEG seizures included assignment to a predominant circulatory arrest strategy or longer duration of circulatory arrest and diagnosis of D-TGA with VSD.

Early transient postoperative clinical seizures have been reported in 4% to 10% of infants with critical congenital heart disease undergoing reparative open heart surgery, and the incidence of seizure activity detected by continuous EEG monitoring during this period is even higher. The outcome of infants with such seizures after open heart surgery has not been previously studied. Using the longitudinal database of the Boston Circulatory Arrest Study, we explored the relationship between clinical and EEG seizures in the early postoperative period and subsequent neurological and developmental outcomes at ages 1 and 2½ years. We further assessed whether the characteristics of EEG seizures, such as duration and cerebral location of seizure onset, were related to these outcomes. Finally, because assignment to a circulatory arrest strategy was associated with worse neurological function and motor skills at age 1 year and poorer language skills at age 2½ years, we investigated whether seizure occurrence was an independent risk factor for worse neurodevelopmental outcome after adjustment for support strategy.

Methods

Subjects

Between April 1988 and February 1992, we enrolled 171 patients in a prospective, randomized, single-center trial. Eligibility criteria in-
included a diagnosis of D-TGA with IVS or VSD, repair by 3 months of age, and coronary artery anatomy considered suitable for the arterial switch operation. Exclusion criteria included a birth weight <2.5 kg, a recognizable syndrome of congenital anomalies, associated extracardiac anomalies of greater-than-minor severity, previous cardiac surgery, or associated cardiovascular anomalies requiring aortic arch reconstruction or additional open surgical procedures. We obtained informed consent from the parents of all subjects. Additional information about the study design, perfusion methods, surgical techniques, and anesthetic management is presented elsewhere.9

Clinical Seizures
The criteria for diagnosis of a clinical seizure, made by bedside nurses and physicians, included single or recurrent motor events involving extremity or cranial nerve muscle movements that were associated with alterations of consciousness and not interruptible by manipulation of the body part involved. Isolated apneic or tachycardiac episodes, isolated eye movements, and sucking or tongue movement abnormalities alone were not considered definitive evidence of a seizure.1

Video EEG Monitoring
The technique and methods for EEG interpretation have been previously described.1,2,11 In brief, we classified rhythmic paroxysmal activity on EEG recordings from the first 48 postoperative hours as ictal (ie, EEG seizure activity) if the total duration of discharge exceeded 5 seconds; this arbitrary definition was chosen to ensure that brief seizures would not be overlooked. The total duration of ictal activity and localization of the onset were also recorded. A total of 136 infants underwent EEG monitoring. For the remaining infants, either the EEG machine was unavailable or parents declined monitoring. The median total duration of ictal activity was 139 minutes (range, 6 seconds to 980 minutes). Only 1 of the 27 patients with EEG seizures had seizure duration between 5 and 10 seconds. EEG seizure onset was most common in the central (16 infants, 59%) or frontal (11 patients, 41%) regions.2 Clinical seizures were detected in only 9 of 27 infants (33%) with EEG seizures. In contrast, EEG seizures were detected in all 9 patients with clinical seizures in whom simultaneous EEG monitoring was performed. In the other 2 children with clinical seizures, EEG monitoring was not ongoing at the time of the seizures.2

One-Year Assessments
Of the 171 infants enrolled in the trial, 168 were alive at age 1 year, and 155 (92%) returned for evaluation.8 Characteristics of children who returned at 1 year of age are given in Table 1.

We administered the Bayley Scales of Infant Development,12 which yield the PDI and MDI. The PDI tasks examine gross and fine motor function, whereas the MDI tasks examine cognitive functioning. We also used the Bayley mental scale item analysis method of Kohen-Raz13 to characterize children’s performance in specific developmental domains.13 In addition, the proportions of children who were assigned a score of “pass” on the following three motor scale items were determined: neat pincer (fine prehension), pat-a-cake (midline skill), and walks alone at 1 year. These items were selected for analysis because they represent important milestones of fine and gross motor development. In the cohort at age 1 year, the mean PDI score was 95.1±15.5, and the mean MDI score was 105.1±15.0.

A board-certified pediatric neurologist performed blinded neurological examinations using a format derived from the National Collaborative Perinatal Project.7 Neurological function was classified as normal, possibly abnormal, and abnormal. In the cohort who returned at age 1 year, 5 children (3%) had possible abnormalities and 48 (31%) had definite abnormalities, all of which were judged to be mild in severity. A total of 28 children (18%) had hypotonia, 7 (5%) had cerebral palsy, 4 (3%) had focal abnormalities, and 2 (1%) had abnormalities of special senses.8

Patients also underwent MRI of the brain.8 In the cohort, 33 patients (23%) had abnormalities (11 with possible abnormalities and 22 with definite abnormalities). Abnormalities were classified as focal or multifocal in 20 children (14%), diffuse in 16 (11%), and developmental or incidental in 3 (2%).8

Developmental Questionnaires at Age 2½ Years
Parents were contacted by mail and asked to complete three questionnaires about their child’s development and behavior: the Minnesota Child Development Inventory,14 the MacArthur Communicative Development Inventory/Words and Sentences,15 and the Child Behavior Checklist/2 to 3.16 These instruments, the response rates, and the dependent variables analyzed have been previously described.8 Analyses of the Minnesota Child Development Inventory are based on 106 children; of the MacArthur Communicative Development Inventory, on 90 children; and of the Child Behavior Checklist/2 to 3, on 113 children.

Statistical Analyses
Primary analyses compared the neurodevelopmental outcomes of infants who had postoperative clinical or EEG seizures to those who had not. Outcomes at ages 1 and 2½ years included both continuous and categorical variables. T tests, 95% CIs for the mean difference between two groups, and linear regression methods were used to

### TABLE 1. Characteristics of Children With D-TGA Who Returned for Evaluation at 1 Year of Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative characteristics</th>
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<tbody>
<tr>
<td></td>
<td>Birth weight, g</td>
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<td>Gestational age, wk</td>
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<td>Apgar score at 5 min</td>
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<td>Age at surgery, d</td>
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<td>Surgical data</td>
<td>Circulatory arrest, min</td>
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<td>Total bypass time, min</td>
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<td>Total support time, min</td>
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<td>Postoperative seizure abnormalties, n/total (%)</td>
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<td></td>
<td>Clinical seizures within 7 days</td>
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<td></td>
<td>EEG ictal activity within 48 hours*</td>
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<td></td>
<td>Follow-up data at 1 year</td>
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<td>Weight (z score)</td>
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<td>Length (z score)</td>
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<tr>
<td></td>
<td>Social class†</td>
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<tr>
<td></td>
<td>Maternal IQ‡</td>
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</tbody>
</table>

Values are mean±SD when appropriate.
*Rhythmic epileptiform activity continuing for >5 seconds on continuous video EEG monitoring.
†Score on the Hollingshead Four-Factor Index of Social Status.
‡Score on the Peabody Picture Vocabulary Test-Revised.
analyze continuous outcomes. Fisher’s exact tests and logistic regression methods were used to analyze categorical outcome variables. In secondary analyses restricted to infants with EEG seizures, we compared the outcomes of those whose total duration of EEG seizures was greater than the median duration (139 minutes) to outcomes of those with seizures of lesser duration, and the outcomes of those who had at least one seizure onset in the frontal lobe to the outcomes of those without. We also compared outcomes of infants with EEG seizures in whom clinical seizures were manifest to outcomes of those in whom clinical seizures were not noted; although infants with both EEG and clinical seizures tended to have worse outcomes than those with EEG seizures alone, the differences did not achieve statistical significance (all P>.10), so the results are not presented here. In all analyses, we omitted one infant who had a clinical seizure after a cardiac and respiratory arrest 9 days after his arterial switch operation. This late cardiac and respiratory arrest, rather than intraoperative events, was judged to be the cause of the presumed hypoxia-related seizure.

In previous analyses, worse developmental and neurological outcomes were associated with longer duration of total circulatory arrest during open heart surgery or with an associated diagnosis of a VSD. Therefore, we used multiple regression to assess whether adjusting for these two variables altered the estimated association between seizures and later outcomes.

**Results**

**Psychomotor Development Index**

Children with seizures had lower PDI scores than children without seizures (for clinical seizures: 12.9 MD; 95% CI, 2.2 to 23.6; P=.02; for EEG seizures: 13.3 MD; 95% CI, 6.8 to 19.7; P<.001; Table 2). Among infants with EEG seizures, those with longer total duration of seizures (>139 minutes) tended to have lower PDI scores than those who did not (10.3 MD; 95% CI, −1.7 to 22.3; P=.09). Similarly, PDI scores tended to be lower among infants in whom at least one seizure had a frontal onset (10.3 MD; 95% CI, −1.7 to 22.3; P=.09). Among the 25 infants with EEG seizures who came back for the 1-year evaluation, those with longer total duration of seizures (>139 minutes) were more likely to have had at least one seizure with a frontal onset compared with those with shorter total duration of seizures (≤139 minutes) (64% versus 21%, P=.05). This strong association between longer seizure duration and frontal onset prevented us from determining which was more predictive of poorer outcome.

PDI scores of ≤80, approximately 2 SD or more below the contemporary mean score on the 1969 version of this test, were more common among children with seizures than among those without seizures (for clinical seizures: 63% versus 17%, P=.007; for EEG seizures: 56% versus 13%, P<.001; Table 3). Among infants with EEG seizures, total duration and location of seizure onset were not significantly associated with PDI score ≤80.

**Mental Development Index**

The MDI scores of children with clinical or EEG seizures were lower than those of children without seizures, but the differences were not statistically significant (for clinical seizures: 6.8 MD; 95% CI, −3.8 to 17.5; P=.21; for EEG seizures: 5.7 MD; 95% CI, −2.7 to 14.1; P=.18; Table 2). Among infants with EEG seizures, longer total duration of seizures tended to be associated with lower MDI scores (13.7 MD; 95% CI, −1.8 to 29.2; P=.08). Although mean MDI scores were lower in those children in whom at least one seizure had a frontal onset, the difference did not achieve statistical significance (12.5 MD; 95% CI, −3.2 to 28.2; P=.11).

MDI scores of ≤80 were more common in children with EEG seizures than in those without seizures (13% versus 2%; P=.05; Table 3) and tended to be more common in children with >139 minutes of EEG seizures (P=.06).

**Kohen-Raz Scoring of Bayley Scales**

Subjects with EEG seizures had worse scores than those without EEG seizures on the eye-hand coordination (0.7 MD; 95% CI, 0.0 to 1.4; P=.04), object relations (0.5 MD; 95% CI,
Neurological Examination

Infants with seizures were more likely to have an abnormal neurological examination (for clinical seizures: 78% versus 31%, \(P = .008\); for EEG seizures, 58% versus 34%, \(P = .04\); Table 4). Among infants with EEG seizures, neither the total duration of EEG seizures nor frontal location of EEG seizure onset was associated with increased risk of an abnormal examination.

Magnetic Resonance Imaging

Clinical seizures were not associated with MRI abnormalities. Children with EEG seizures were more likely to have MRI abnormalities than were children without EEG seizures (43% versus 13%, \(P = .002\); Table 4). Among infants with EEG seizures, neither the total duration of EEG seizures nor frontal location of EEG seizure onset was associated with increased risk of an abnormal MRI.

Questionnaires at Age 2\(\frac{1}{2}\) Years

Children with EEG seizures had lower scores on three of the eight scales of the Minnesota Child Development Inventory. These areas were general development (7.8 MD; 95% CI, 0.5 to 15.1; \(P = .04\)), expressive language (5.3 MD; 95% CI, 1.7 to 8.9; \(P = .005\)), and personal-social (2.0 MD; 95% CI, 0.2 to 3.8; \(P = .03\)). EEG seizures were also associated with worse scores on five of seven scales and a tendency toward lower scores on the other two scales of the MacArthur Communicative Development Inventory. These included vocabulary production (139.4 MD; 95% CI, 24.3 to 254.4; \(P = .02\)), irregular forms (4.9 MD; 95% CI, 1.0 to 8.8; \(P = .01\)), overregularization (2.9 MD; 95% CI, 0.6 to 5.1; \(P = .01\)), sentence complexity (10.6 MD; 95% CI, 4.3 to 16.9; \(P = .001\)), the mean length of utterance in morphemes of the three longest sentences heard recently (2.4 MD; 95% CI, 0.2 to 4.6; \(P = .03\)), word use (0.5 MD; 95% CI, −0.1 to 1.1; \(P = .09\)), and word endings (0.9 MD; 95% CI, −0.1 to 1.8; \(P = .07\)). Parent-described behavior problems on the Child Behavior Checklist were not associated with clinical or EEG seizures.

Localization of Seizure Onset and Seizure Predominance

We examined the associations of initial site of seizure onset or predominant site of seizure onset with site of MRI abnormalities or specific developmental problems. Sites of MRI abnormalities were not significantly associated with sites of seizure onset or predominance. Similarly, there were no significant associations between site of first seizure onset or predominant site and specific developmental deficits either on the Kohen-Raz subscales at 1 year of age or the subscales of the Minnesota or MacArthur scales at 2\(\frac{1}{2}\) years of age.

Adjustment for Circulatory Arrest and Diagnosis

We have previously reported that longer duration of circulatory arrest and associated diagnosis of VSD were significantly associated with lower PDI scores at age 1 year. To explore whether seizure occurrence was an independent risk factor for worse neurodevelopmental outcome, we performed analyses adjusting for duration of circulatory arrest and diagnosis (ie, D-TGA with IVS or VSD). EEG seizures remained significantly associated with lower PDI scores (11.5 MD; 95% CI, 4.8 to 18.2; \(P = .001\)), with an increased risk of having a PDI...
TABLE 4. Possible or Definite Neurological and MRI Abnormalities as a Function of Seizure Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neurological Abnormalities</th>
<th>MRI Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. With Abnormality/Total (%)</td>
<td>P*</td>
</tr>
<tr>
<td>Clinical seizures within 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45/144 (31)</td>
<td>.008</td>
</tr>
<tr>
<td>Yes</td>
<td>7/9 (78)</td>
<td></td>
</tr>
<tr>
<td>EEG ictal activity within 48 hours†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34/100 (34)</td>
<td>.04</td>
</tr>
<tr>
<td>Yes</td>
<td>14/24 (58)</td>
<td></td>
</tr>
<tr>
<td>Among children with EEG ictal activity within 48 hours†</td>
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<td></td>
</tr>
<tr>
<td>Total duration of EEG seizures, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤139</td>
<td>7/14 (50)</td>
<td>.42</td>
</tr>
<tr>
<td>&gt;139</td>
<td>7/10 (70)</td>
<td></td>
</tr>
<tr>
<td>Location of EEG seizure onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never frontal</td>
<td>8/14 (57)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever frontal</td>
<td>6/10 (60)</td>
<td></td>
</tr>
</tbody>
</table>

*P calculated from Fisher’s exact test.
†Rhythmic epileptiform activity continuing for >5 seconds on continuous video EEG monitoring.

At 2 1⁄2 years of age, EEG seizures remained significantly associated with worse performance on one of the scales on the Minnesota Child Development Inventory, expressive language (4.2 MD; 95% CI, 0.5 to 7.8; P=.03), and four of seven scales of the MacArthur Communicative Development Inventory (vocabulary production, P=.008; word endings, P=.04; irregular forms, P=.05; sentence complexity, P=.005) and was marginally related with scores on the other three scales (word use, P=.06; overregularization, P=.10; mean length of utterance, P=.07).

**Discussion**

We found that in infants undergoing the arterial switch operation within the first 3 months of life for correction of D-TGA, postoperative clinical and EEG seizures were associated with a consistent pattern of worse developmental and neurological function at 1 and 2 1⁄2 years of age. In addition, EEG seizures were associated with MRI abnormalities. Longer total duration of EEG seizures was also marginally associated with an increased risk of delayed motor and mental development at 1 year of age. The magnitude of these relationships was moderate but consistent across outcome variables, with the most marked differences at 1 year of age between children with and without early seizures being on the PDI, which measures motor abilities. The pattern of neurodevelopmental delays associated with postoperative seizures persisted as assessed by parent questionnaire at 2 1⁄2 years, with particular problems in language development noted in those children with EEG seizures. Although developmental scores at 1 year of age have low predictive validity for future cognitive function,17,18 the persistence of deficits at 2 1⁄2 years of age provides more convincing evidence of significant impairment of later functioning in infants with postoperative seizures.

The relationship between postoperative clinical seizures and developmental and neurological outcome has been controversial. There is considerable evidence from experimental studies that prolonged seizures lead to damage in mature animals. In a seizure, as in hypoxic-ischemic injury, excessive release of excitatory amino acids leads to stimulation of glutamate receptors with subsequent increases in intracellular calcium and sodium.19–24 The immature brain may be more susceptible to overstimulation of excitatory amino acid receptors. Autoradiographic binding studies show that in many regions, the immature rodent brain has more glutamate receptors than the mature rodent brain.25 This may be true in the human brain as well.26 In contrast, multiple animal studies have demonstrated that the immature brain is less vulnerable to seizure-induced damage than is the mature brain. Studies with several animal models using kainic acid,27–30 pilocarpine,31 and hippocampal stimulation32 have shown that prolonged seizures in the immature animal are associated with fewer histological lesions and behavioral abnormalities than are similar induced seizures in mature animals.

Several clinical studies have shown that children with neonatal seizures from various causes have worse developmental and neurological outcomes than do those without seizures.33–37 The cause of the worse neurodevelopmental
outcome is unknown, and it is uncertain whether the seizures reflect previous brain damage, cause brain damage, or both. Both hypoxia/ischemia and seizures can stimulate receptor-mediated excitotoxicity, especially in the immature brain, producing injury to the parts of the brain that are most vulnerable and are developing most rapidly.20-24 We could hypothesize that at the time of the operation, the most actively developing areas control motor development and precursors to language development. While there are multiple mechanisms in the brain to protect it from such damage, these defenses can be overwhelmed. Johnston25 has called this type of damage a “synaptic power surge” carried by ions such as calcium that cause neurotoxicity.

Because most cardiac postoperative seizures do not persist, recur, or cause striking developmental sequelae, questionable prognostic importance has been attributed to them. Our data, however, suggest that both clinical and EEG seizures are important risk factors for future developmental and neurological problems. In fact, seizures might be used as an early surrogate variable for worse neurodevelopmental outcome in future trials of strategies for protecting neurological function, potentially reducing the time until end points with prognostic significance can be measured.

Previous studies describing continuous EEG monitoring of newborns in clinical situations have reported the onset of EEG seizure activity to be predominantly in the temporal and central regions.39,40 In contrast, almost half the infants in our cohort had one or more seizure onsets in the frontal region. The reason that seizures of frontal onset occurred with such high frequency in our population is uncertain. Surface cooling during infant cardiac surgery is achieved by packing ice on the sides, top, and posterior portions of the head but usually does not include the anterior portions of the frontal region. It is possible that this cooling strategy leads to unequal cooling and increased vulnerability of the frontal area to the effects of hypoxia. In our cohort, infants who had seizures of frontal onset tended to have worse outcomes than did infants with either no seizures or seizures with nonfrontal onset. The strong association between the presence of frontal onset seizures and longer total duration of seizures precluded determination of the independent contributions of these variables.

Certain study limitations should be noted. Although developmental test scores at 1 year of age have strong concurrent validity and provide valid descriptions of mental and motor performance at this age, their predictive validity for later intelligence or academic deficits is low. At 2½ years, we were dependent on parents’ descriptions of children’s performance, which are not as reliable as direct testing. In addition, our response rate was decreased at age 2½ years, so a volunteer effect may have biased the data. Finally, the very small number of subjects with clinical seizures limited our statistical power to detect effects on some 1-year outcomes, and the relatively small number of subjects with EEG seizures limited our power to evaluate relations between site of onset and predominance and specific deficits.

In summary, transient seizures detected both clinically and by continuous video EEG monitoring in the first postoperative 48 hours were associated with a pattern of worse developmental and neurological outcomes at 1 year and worse develop-

mental and particularly language outcomes at 2½ years. Future studies should explore whether the use of prophylactic anticonvulsant treatment can prevent the occurrence of seizures and whether treatment of EEG seizures alters later neurodevelopmental outcome. We are currently completing analysis of our study cohort at age 4 years to more fully investigate the relationship of postoperative seizures to long-term outcomes.

Acknowledgments
This work was supported by grants HL-41786, RR-02172, and P30-HD-18655 from the NIH. We are indebted to Lewis Kull, Sheila A. McPeck, Susan M. Hegarty, and Wayne A. Cote for EEG technology; to Ludmila Kyn for database and statistical programming; to the nursing staff for assistance in protocol adherence; to Donna M. Donati, Donna M. Duva, and Lisa-Jean Buckley for data management; and to Kathleen M. O’Brien for project coordination. Other members of the Boston Circulatory Arrest Study Group include Paul R. Hickey, MD; James H. Ware, PhD; Jules Constantinnou, FRACP; Emmanuel Carrazana, MD; John C. Share, MD; David E. Wessel, MD; Frank L. Hanley, MD; John E. Mayer, Jr, MD; Aldo R. Castaneda, MD; David M. Farrell, MA, CCP; Patrick D. Barnes, MD; Roy D. Strand, MD; Amy Z. Walsh, RN, BSN; and Christine Plumb, RN, MSN.

References
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Circulation. 1998;97:773-779
doi: 10.1161/01.CIR.97.8.773

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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