SIGNIFICANCE OF ELECTROENCEPHALOGRAPHIC CHANGES OCCURRING DURING CARDIOPULMONARY BYPASS

ROBERT E. COONS, M.D., ARTHUR S. KEATS, M.D., DENTON A. COOLEY, M.D.

THE ELECTROENCEPHALOGRAM has been demonstrated to be a sensitive and valuable monitor during clinical anesthesia. Is has been used as a guide to depth of anesthesia,[1] and as an early indicator of hypoxia,[2] hypotension,[3] and carbon dioxide accumulation.[4] It was to be expected that the electroencephalogram would prove to be an important monitor in the regulation of body perfusion during extracorporeal circulation.[5, 6]

In the first two years during which open heart surgery with low flow (35–50 cc./kg./minute) extracorporeal circulation was performed at this institution, approximately 300 patients with acquired and congenital heart disease were operated on with a high degree of success without the benefit of an electroencephalographic monitor. Recently we acquired an electroencephalograph suitable for operating room use and have been able to observe the changes which had probably occurred in the previous 300 patients. Since clinically evident cerebral anoxia had not been observed postoperatively in any previously operated patients, no alteration in technique or perfusion rates were made as a result of the acquisition of this monitor. Since the operative, anesthetic, and perfusion techniques had become well established and of demonstrated safety, we were able to allow electroencephalographic changes to progress without concern for the patient.

We have collected technically adequate electroencephalographic records of 76 successive patients who have undergone extracorporeal circulation and have correlated the magnitude of encephalographic changes observed during cardiopulmonary bypass with the postoperative mental state of the patient. An analysis of these records provided the basis of this report and indicated that drastic changes in the electroencephalogram can occur and persist for relatively long periods of time without postoperative neurological deficit. These observations provoke questions as to the prognostic significance of electroencephalographic changes attributed to hypoxia and to the supputed sensitivity of the brain to anoxic damage.

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METHODS

All patients in this series underwent open cardiotomy for surgical correction of congenital or acquired cardiac defects. The patients ranged in age from 4 months to 45 years and in weight from 8 to 163 pounds. The anesthetic technique used has been described in detail elsewhere.[7] In brief, all patients were premedicated with pentobarbital, meperidine, and scopolamine in doses which were anticipated to produce deep sleep prior to induction of anesthesia. Anesthesia was induced with cyclopropane and following tracheal intubation ether-oxygen was administered with succinylcholine infusion to maintain apnea. Ether was discontinued about five minutes before cardiopulmonary bypass and no anesthetic agent was administered during bypass. Oxygen alone was used to aerate the blood of the extracorporeal system. Patients were given a single dose of *d*-tubocurare 5 minutes before bypass. After bypass, only oxygen was administered until the patient began to move. Fifty per cent nitrous oxide and oxygen was then administered until the end of the operation.

In all patients a bubble type oxygenator was used, either a stainless steel unit [8] or a disposable plastic type.[9] Infants were perfused at a rate of 50 cc./kg./minute. Adults were perfused at 35 cc./kg./minute. The rest were perfused at 40–45 cc./kg./minute. Perfusion was performed through the femoral artery with venous blood returned to the pump oxygenator from the vena cavae. Induced cardiac arrest was not used. The electroencephalogram and the electrocardiogram were recorded simulta-

neously with a Grass Polygraph, using the left fronto-mastoid lead, with electrodes inserted intracutaneously. The electroencephalogram and electrocardiogram were recorded intermittently before cardiopulmonary bypass but continuously during and after bypass until the electroencephalogram returned to the pattern prior to bypass. Esophageal temperature was recorded throughout the operation.

The mental state (degree of awareness) was estimated immediately before induction of anesthesia and after the end of anesthesia but before the patient left the operating room. Three degrees of awareness could be readily distinguished: (1) Awake: Patients could talk, answer questions, follow commands. Infants were awake and crying. (2) Asleep: Patients did not respond to questions or commands, but possessed all their reflexes and would respond to pain or stimulation by purposeful movement. (3) Deeply Asleep: No response to voice or stimulation, although corneal, swallowing, and coughing reflexes were present. All patients could be classified in these categories, both before and after operation.

Results

Electroencephalographic patterns occurring during and after cardiopulmonary bypass were compared with those obtained immediately prior to bypass under light ether-oxygen anesthesia. Prebypass records were similar to those described by Courtin *et al.*[10] as occurring between electroencephalographic stages 1 and 2 ether anesthesia and to that described by Bellville and Artusio [11] for ether analgesia, except that the dominant activity was 16–20 c.p.s., with a voltage of 20–40 μv. (fig. 1, 2 and 3). The changes during perfusion could be classified into three types:

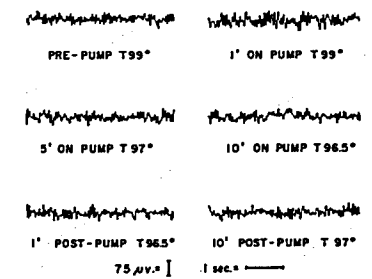

Fig. 1. Group 1. No electroencephalographic change. Electroencephalographic record of an 11 year old male weighing 57 pounds, with an interventricular septal defect. Perfusion rate 40 cc./kg./minute. Dependent time 10.5 minutes; perfusion time 13 minutes. Prior to bypass the activity is 18 c.p.s. and 30–40 μv. Esophageal temperature decreased 2.5 degrees F. during perfusion.

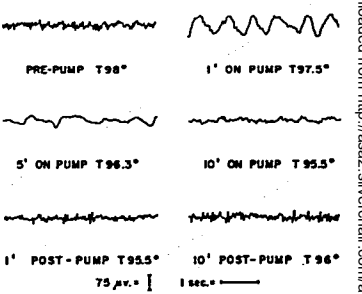

Fig. 2. Group 2. Return of electroencephalographic activity during perfusion. Electroencephalographic record of an 18 year old male weighing 136 pounds, with an interatrial septal defect and anomalous pulmonary veins. Perfusion rate 35 cc./kg./minutes. Dependent time 11 minutes; perfusion time 14 minutes. Prepump pattern was 16 c.p.s., 20–30 μv. One minute after perfusion high voltage 1 c.p.s. activity appeared and decreased in amplitude during perfusion. Some fast activity was present throughout. By 10 minutes following perfusion, the preperfusion pattern had reappeared. Esophageal temperature decreased 2 degrees F. during perfusion.

Group 1: No electroencephalographic change. In 16 patients, the preperfusion electroencephalographic pattern was maintained throughout bypass (fig. 1). Some decrease in amplitude, and at times, a slight decrease in frequency was observed. However, in no patient was there loss of rapid activity or the appearance of delta waves.

Group 2: Return of electroencephalographic pattern. In 19 patients there was an early loss of rapid activity (15 to 45 seconds after vena cavae occlusion) replaced by high voltage slow delta waves at times exceeding 200 μv.

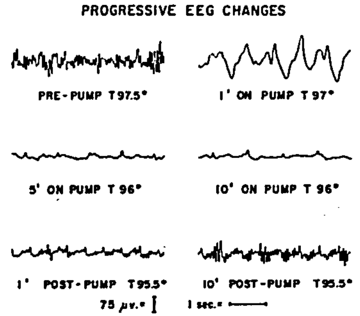

Fig. 3. Group 3. Progressive electroencephalographic changes. Electroencephalogram of a 9 year old female weighing 58 pounds, with pulmonary stenosis. Perfusion rate 40 cc./kg./minute. Dependent time 12 minutes; perfusion time 13 minutes. Prior to bypass there was a rapid (16 c.p.s.) high voltage activity which changed rapidly to high voltage delta activity one minute after perfusion. After 5 minutes of perfusion, little activity was present and artifacts appeared. By 10 minutes of perfusion only ECG artifacts were present, in which P, R, and T waves could be identified. One minute after perfusion, rapid activity had returned and by 10 minutes, a pattern similar to the preperfusion pattern was present.

and slower than 1 c.p.s. Delta activity persisted for 0.5–6 minutes (most commonly 1–3 minutes). Typically, rapid activity began to appear superimposed on the delta rhythm with a gradual replacement of delta rhythm by the preperfusion pattern (fig. 2). Some decrease in amplitude and frequency occurred as well during the period of bypass.

Group 3: Progressive electroencephalographic changes. In 33 patients the pattern of group two promptly appeared with large, slow delta waves. However, instead of a return of rapid activity, progressive flattening of the delta waves ensued, developing into an essentially flat electroencephalogram (fig. 3). The criterion used to determine a "flat electroencephalogram" was based on the electroencephalogram records obtained from 3 patients who expired in the operating room. In these patients the electroencephalogram was recorded after death to estimate the degree of base line variation due to operating room background activity. An example from one such patient is shown in figure 4. In 8 of the 33 records (25 per cent), there were periods which could be described as isoelectric, but these periods were brief (less than 10 seconds). The remainder of the records consisted of baseline variation with electrocardiographic artifacts which could not be distinguished from background activity. In 60 per cent of the records there also appeared transient periods of low voltage rapid activity (10–15 c.p.s. less than 5 µv. and lasting from 1–3 seconds) superimposed on the flat electroencephalogram. Similar activity was seen in portions of EEG records taken after death. Except for the slower frequency, this rapid activity was similar to that described by Pearcy and Virtue[12] as following circulatory occlusion during hypothermia. In 60 per cent of these patients the electroencephalogram remained flat until the end of bypass.

The pertinent characteristics of the patients falling into each of these groups were compared (table 1). The mean age, the mean dependent time (the duration of cardiac inflow occlusion during which the patient was entirely dependent on the pump oxygenator for oxygenation) and the mean decrease in esophageal temperature were approximately the same in all groups. In addition, the mean time re-

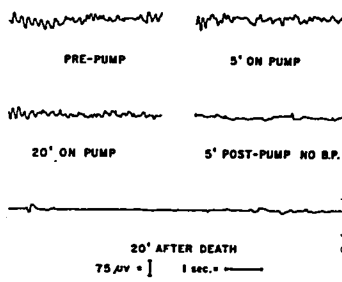

Fig. 4. Electroencephalographic changes in a patient who expired following cardiopulmonary bypass. This patient was a 2 year old child with atrioventricularis communis, who was unable to maintain cardiac output following repair. Electroencephalographic activity was well maintained only during perfusion. Five minutes after perfusion, only ECG artifacts appeared. The electroencephalogram was recorded 20 minutes after death to obtain a tracing of the base line variation in the absence of cerebral activity under operating room conditions, but without any surgical manipulations.

TABLE 1

PERTINENT CHARACTERISTICS OF PATIENTS UNDERGOING CARDIOPULMONARY BYPASS CLASSIFIED ACCORDING TO DEGREE OF ELECTROENCEPHALOGRAPHIC CHANGE DURING PERFUSION

Characteristics	Group 1	Group 2	Group 3
	No EEG Change	Return of EEG	Progressive Change
Number of patients	16	27	33
Age (years)			
Mean ± SE*	10.9 ± 3.3	8.8 ± 1.6	7.0 ± 0.7
(Range)	(0.3–45)	(1.5–45)	(0.7–17)
Dependent time (min.)			
Mean ± SE*	11.4 ± 1.2	11.7 ± 1.1	10.9 ± 0.7
(Range)	(7.0–22)	(5.5–30)	(3.5–20)
Decrease in esophageal temperature (F.)			
Mean ± SE*	4.9 ± 0.4	4.7 ± 0.4	4.5 ± 0.4
(Range)	(1.5–7.5)	(0.5–9.0)	(1.0–12)
Duration of flat EEG (min.)			
Mean ± SE*	—	—	6.24 ± 0.73
(Range)			(0.5–18)
Time of EEG recovery (min.)			
Mean ± SE*	—	14.0 ± 3.7	17.7 ± 3.4
(Range)		(0.5–60)	(0.5–60)
	Per Cent	Per Cent	Per Cent
Degree of awareness:			
Preoperative			
Awake	31	30	36
Deeply asleep	38	33	36
Postoperative			
Awake	44	52	58
Deeply asleep	19	11	12

* Standard error of mean.

quired following bypass for the electroencephalogram to return to its preperfusion pattern was approximately the same in both groups in whom changes occurred during perfusion. Finally, and most significantly, the degree of awareness postoperatively (expressed as per cent of patients who were awake) was not related to the degree of electroencephalographic change observed during perfusion. Preoperatively, approximately one-third of the patients in all three groups were heavily premedicated (deeply asleep) and about one-third were inadequately premedicated. In all groups, 11–19 per cent of the patients were deeply asleep at the end of operation and 44–58 per cent were awake. All patients who were deeply asleep at the end of operation were awake within one hour after arrival in the recovery room. No patient suffered any postoperative neurologic deficit.

The electroencephalographic changes observed in groups 2 and 3 are typical of those described as the result of hypoxia, hypotension, deep anesthesia, and hypercarbia.[12] Assuming the changes observed here were the result of stagnant hypoxia associated with a subnormal cerebral blood flow, one would expect a significant correlation between several of the observations made. One would expect a significant correlation between the dependent time and the time for the electroencephalogram to return to the preperfusion pattern. This was not the case. In groups 2 and 3 the correlation coefficients were respectively $r = 0.17$ ($P < 0.4$) and $r = 0.19$ ($P < 0.2$).[14] Similarly, the correlation coeffi-

cient in group 3 between the duration of flat electroencephalogram and the time for electroencephalographic recovery was not significant ($r = 0.03$, $P = 0.5$). A similar lack of correlation existed between the degree of electroencephalographic change and the degree of awareness postoperatively. In group 3, the 4 patients who were most deeply asleep at the end of the surgical procedure had a flat electroencephalogram for a mean of 6.0 minutes. The 19 patients in the same group who were awake postoperatively had a flat electroencephalogram for 6.4 minutes. Similarly, the 7 patients in whom the electroencephalogram was flat for from 10 to 18 minutes were as alert postoperatively as the 10 patients in whom the electroencephalogram was flat for 1–3 minutes. Obviously, the degree of awareness and the rate of electroencephalographic recovery were not related to the degree of electroencephalographic change observed during cardiopulmonary bypass. The electroencephalographic pattern was also not related to the perfusion rate between 35 and 50 cc./kg./minute, nor to the absolute values of flow.

Discussion

It is immediately apparent from these observations that widely differing electroencephalographic patterns appeared despite the use of approximately the same flow rates for total body perfusion calculated on an age-weight basis. Unless one postulates great differences in rates of cerebral oxygen demand among patients, which is unlikely, the most likely explanation lies in the varying percentage of total perfused blood which reached the brain. Assuming that all factors in the extracorporeal system which could affect delivered blood flow were kept constant (*e.g.*, resistance in the tubing and cannulae, complete occlusion in the pumping system, and accuracy in the techniques of measuring flow during perfusion), it is still unlikely that the resistance in all body vascular beds would be identical during total body perfusion. It is therefore probable that in those patients in whom no significant electroencephalographic changes were observed, a larger proportion of perfused blood went to the cerebral circulation as a result of increased resistance in other vascular beds.

Several mechanisms may be postulated to explain the electroencephalographic changes in group 2 in which, after initial marked changes, there was a return of rapid activity during perfusion. Schallek and Walz[15] have demonstrated that low arterial blood pressure can be reached without electroencephalographic changes if blood pressure is gradually reduced, whereas marked changes occur during a rapid decrease in blood pressure. Therefore, the initial loss and return of electroencephalographic activity may be related to the adjustment of the cerebral blood vessels to the sudden pressure change induced by cardiopulmonary bypass. It is also possible that the return of activity was the result of the mild hypothermia and decreased cerebral oxygen demand induced by the cool blood of the extracorporeal circuit. However, patients in group 3 were cooled to a similar degree without return of electroencephalographic activity. It has also been postulated that this initial change to delta rhythm is the result of the direct effect of cold blood on the cerebral vessels, since the early appearance of delta waves and return of rapid activity has also been observed in patients perfused at much higher calculated flow rates.[6] Another possibility is the progressive increase in total peripheral resistance which has been observed during cardiopulmonary bypass.[16] This may result in the shunting of an increasing portion of total blood flow to the cerebral circulation. Finally, the return of the electroencephalographic activity may simply represent the capacity of the cerebral circulation to regulate its own flow in a compensatory response to local metabolic changes.

The third group of 33 patients with progressive deterioration of the electroencephalogram and with varying periods of absent activity is most interesting. The most likely cause of these changes is stagnant hypoxia from subnormal cerebral perfusion. If this were so, one would expect some correlation between the severity of changes observed and the rapidity of electroencephalographic recovery following perfusion or the rapidity of awakening postoperatively. Clearly there was no correlation and no patient demonstrated any postoperative signs or symptoms known to follow cerebral hypoxia. Since the duration of pe

fusion in these patients did not exceed 22 minutes, nor the duration of flat electroencephalogram exceed 18 minutes, it is possible that some sequelae would have been observed if these changes persisted for a longer period of time. However, it is just as likely that there exists a level of cerebral perfusion during which no electroencephalographic activity is apparent, but during which there is sufficient tissue oxygenation to prevent cellular damage. This may be so, since the electroencephalograph is an extremely sensitive, but nonspecific, indicator of cerebral function. Because of its extreme sensitivity it may lose value when used to measure a graded response such as cerebral perfusion. An analogy in reverse would be the electrocardiogram which continues to record when no effective circulation exists. Because of this high sensitivity, the electroencephalogram may give no information in the area between a flat electroencephalogram with complete recovery and a flat electroencephalogram with irreversible tissue damage.

It would seem from these observations that the use of a normal electroencephalographic pattern as the criterion for adequate cerebral perfusion and as a guide in the regulation of extracorporeal perfusion rates is neither necessary nor desirable. A reasonable criterion for adequate and safe cerebral perfusion during extracorporeal circulation would be the presence of some electroencephalographic activity during perfusion, more than flat and less than prior to perfusion. The increased trauma to the blood, the increased complexity of the extracorporeal apparatus required, and the larger amounts of blood necessary for high perfusion rates make lower perfusion rates more desirable, provided adequate cerebral circulation can be assured.

These observations do not detract from the value of the electroencephalogram as a monitor during clinical anesthesia. Indeed we, as others, have found that it is most useful in determining when hypotension from blood loss, bradycardia, or obstructed circulation has reached dangerous levels. We continue to use the electroencephalogram during open heart surgery, however not as a guide for the regulation of perfusion rates.

Summary

The electroencephalographic records of 76 patients who have undergone open heart surgery with extracorporeal circulation at low flow perfusion rates (35–50 cc./kg./minute) have been reviewed. At the same calculated rates of perfusion, the electroencephalographic pattern either remained unchanged or showed initial deterioration followed by recovery during perfusion, or showed changes which progressed to an absence of discernible electroencephalographic activity for periods up to 18 minutes. Patients were divided into three groups according to degree of electroencephalographic change observed. There were no differences among these groups in the rate at which the electroencephalogram returned to its perfusion pattern, nor in the degree of awareness exhibited by these patients in the immediate postoperative period. It is postulated that a level of cerebral perfusion exists during which encephalographic activity cannot be identified, but during which hypoxic tissue damage does not occur.

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FIBRINOGEN DEFICIENCIES Diagnosis of fibrinogen deficiencies or fibrinolysis must be suspected in any case of hemorrhage of undetermined etiology in obstetrics. In suspected cases the clot observation test should be performed. A 5 ml. sample of maternal blood is placed in a 15 ml. test tube and gently agitated 4–5 times, then observed for clotting. The clotting mechanism is defective if there is no clot within six minutes or if a clot forms which allows lysis within twelve hours. In suspected cases the attending physician should (1) obtain blood for typing and cross matching, (2) perform clot observation tests, (3) establish a dependable intravenous avenue for administration of whole blood, (4) administer intravenous fibrinogen when indicated until the blood clot is stable, (5) initiate antiheparin and or fibrinolysin therapy as indicated, and (6) manage labor so as to expedite it. (*Longo, L. D., Cailouette, J. C., and Russell, K. P.: Fibrinogen Deficiencies in Pregnancy, Obst. & Gynec. 14: 97 (July) 1959.*)