A Perfluorocarbon Emulsion Prime Additive Improves the Electroencephalogram and Cerebral Blood Flow at the Initiation of Cardiopulmonary Bypass

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ABSTRACT

Depression in electroencephalogram (EEG) has been documented clinically and is reproducible in swine at the initiation of cardiopulmonary bypass (CPB) utilizing a crystalloid prime. The physiological cause of this transient alteration in electrical brain activity appears to be associated with the transient drop in arterial pressure. The etiology is unknown but may be attributable to the bolus of the crystalloid prime or micro emboli, either air or fibrin-platelet.

Thirteen swine (17-26 kg) were anesthetized and received 4 mg/kg dexamethasone, and following a tracheotomy were ventilated with halothane in 100% O₂. Surgical preparation included: sternotomy and preparation for right atrial - aortic CPB. The CPB circuit consisted of a hollow fiber membrane oxygenator, a hard-shell venous reservoir, a roller pump, and PVC tubing. The circuit was randomly primed with either 1200 ml Plasmalyte-A or 10 ml/kg perfluorocarbon emulsion (PFE) and Plasmalyte-A to total 1200 ml. The animals were monitored continuously for systemic hemodynamics and electrocardiogram, and cerebral monitoring included blood flow and bitemporal EEG. Arterial blood gases were measured and PaCO₂ was kept between 30-45 mmHg both before and during CPB. Cerebral blood flow (CBF) was measured pre-CPB and at 10 minutes after initiation of CPB. Bitemporal computerized EEG was analyzed every 60 seconds. Total power of each hemisphere, power in frequency bands, and spectral edge were recorded.

All animals demonstrated a relative decrease in EEG total power at the onset of CPB. Animals that received PFE demonstrated a more stable arterial blood pressure, an increased CBF, and a lesser decrease and an earlier recovery of the EEG power. The differences in hemodynamics and EEG in the PFE prime group may be beneficial in decreasing the neuro-psychological changes associated with CPB and needs further investigation.

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INTRODUCTION

More than 400,000 cardiac procedures requiring cardiopulmonary bypass (CPB) are performed in the United States each year. Definite stroke only occurs in 2-5% of these patients; however, the incidence of more subtle postoperative neuropsychologic or cognitive dysfunction has been documented to approach 30-40% (1-5). Multiple factors have decreased the incidence of neuropsychologic dysfunction including a better understanding of the physiology of non-pulsatile flow, the selected use of hypothermia, and improved equipment (i.e., membrane oxygenators, centrifugal pumps, and arterial filters) (5-7). In spite of improvements such deficits remain a significant perioperative problem and a challenging frontier of cardiac surgery.

While performing experiments to study the ability of a perfluorocarbon emulsion (PFE) to prevent or inhibit the effects of a massive air embolism, we noted a significant, sudden suppression of electroencephalogram (EEG) activity at the onset of CPB. A decrease in EEG activity at the onset of CPB has been previously documented (8). Whether or not this transient depression is clinically significant has yet to be determined. It would seem however that an intraoperative adjunct which could easily be incorporated within an extracorporeal circuit and could eliminate or reduce this depression would be beneficial for the prevention or amelioration of the neurological deficits attributed to CPB.

The purpose of this study was to investigate what effect, if any, a PFE additive to the priming solution of the CPB circuit would have on the EEG at the onset of CPB. The study was designed to measure and record EEG at 1 minute intervals for the first 10 minutes of CPB and to measure cerebral blood flow pre CPB and at 10 minutes after initiation of CPB.

MATERIALS AND METHODS

All experiments were performed in accordance 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 (NIH Publication No. 86-23, revised 1985).

Thirteen farm pigs (17.0-26.0 kg - range; 20.8 kg - avg.) were chemically restrained with a mixture of ketamine (22 mg/kg), acepromazine (1.1 mg/kg), and atropine (0.05 mg/kg). Following tracheotomy, the animals were mechanically ventilated with a Harvard respirator and anesthesia was maintained with halothane in 100% O2. Arterial and venous transmural catheters, used for monitoring arterial blood pressure and to administer intravenous fluids, were then inserted under direct vision and 4 mg/kg dexamethasone (a standard therapy to prevent a species specific vasoactive response to PFE) was administered.

A median sternotomy was then performed and the pericardium opened longitudinally and heparin sulfate (3 mg/kg) was administered. A 20 gauge angiocath was inserted in the right common carotid artery (to be used for air injection later in the experiment) and a polyethylene catheter was placed in the left atrium (to be used for microsphere injection prior to and after CPB). The ascending aorta was cannulated with a 5 mm arterial cannula and the right atrium with a single 28 fr. venous cannula. The CPB circuit consisted of a hollow fiber membrane oxygenator, a hard shell venous reservoir, a roller pump, and PVC tubing; an arterial filter was not utilized. After randomization, the circuit was primed with either 1200 ml Plasmalyte-A (P-lyte group) (n=6) or 10 ml/kg PFE and Plasmalyte-A to a total volume of 1200 ml (PFE group) (n=7). The animals were monitored continuously for systemic arterial blood pressure, bitemporal EEG, and ECG. Paco2 was kept between 30-45 mmHg both before and during CPB. CPB flow rates were 70-80 ml/kg and normothermia was maintained for all animals. No plasma expanders, diuretics, or vasoactive drugs were used in these experiments. One hundred percent O2 was used throughout CPB; mechanical ventilation was stopped at one minute after initiation of CPB.

Cerebral blood flow (CBF) was calculated from microsphere injections made prior to CPB and at 10 minutes after initiation of CPB. Microspheres were injected via a left atrial polyethylene catheter after cannulation but prior to the initiation of CPB and via the arterial line (at the connector of the aortic cannula) during CPB. Microspheres were injected and blood and tissue samples were collected according to the manufacturer’s protocol. Microsphere counts were determined by an independent laboratory.

Bitemporal computerized EEG was analyzed utilizing a Lifescan monitoring system. Total EEG activity of each hemisphere, power in frequency bands, was recorded every 60 sec-

<table>
<thead>
<tr>
<th>Table 1. EEG total power.</th>
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<tr>
<td>Group</td>
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<tr>
<td>P-Lyte</td>
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<tr>
<td>PFE</td>
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<tr>
<td>P Value (unpaired t-Test)</td>
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</table>

Total EEG power is measured in hertz/second and is the sum of activity in both hemispheres.

Interpretation: (p<0.05 for statistical significance).
(a) 1* CPB nearly statistical significance between groups.
(b) 10' CPB statistical significance between groups.
RESULTS

An abrupt decline in the EEG power was observed in all animals at the initiation of CPB. The decrease in the P-lyte group was to 51% of baseline. In animals that received PFE the decrease was only to 71% of baseline (Table 1).

EEG total power, or in other words, the sum of the amplitudes corresponding to each of the four frequency bands; delta, theta, alpha and beta did not differ for the right brain as compared to the left brain over one minute periods of data compression nor did the EEG differ on the left as compared to the right at any other time point within the P-lyte group or within the PFE group during the first 10 minutes of bypass. Therefore, the total power was averaged for the left and the right brain. This average represents values for the "whole brain" for which there was no significant difference between the baseline (pre-CPB) P-lyte group (3112.7 ± 1070.7, n=6) vs. the PFE group (3371.1 ± 426.8, n=7) (See Table 1 and Figure 1).

One minute after initiation of CPB, a nearly statistically significant difference (p=0.07) in EEG power was noted in the PFE primed group (2443.9 ± 932.7) when compared to the P-lyte primed group (1524.3 ± 671.9), a decline which corresponds to 71% of baseline in the PFE group vs. only 51% in the P-lyte group. The decline in EEG power resulted in a level that was also different from baseline within each group (p=0.0001, ANOVA repeated measures).

Two to three minutes into CPB, there was no statistically significant difference in EEG power in either group although the trend persisted. Four minutes into CPB, the difference in the P-lyte vs. the PFE primed groups approached a significant level (p=0.056). Five minutes through 10 minutes into CPB, the difference in the P-lyte as compared to the PFE primed groups was statistically significant (p < 0.05). At ten minutes, the EEG power in the PFE group (2548.1 ± 855.6) was sustained at 75% of baseline as compared the P-lyte group (1550.6 ± 572.8) at 54% of baseline (See Table 1 & Figure 1).

Cerebral blood flow as measured by colored microspheres is shown in Table 2. Pre CPB, a statistically significant difference in cerebral blood flow was noted between the two groups as well as at the 10 minute point. The difference between the pre CPB and the 10 minute measurement within each group also demonstrated statistical significance and this is most noteworthy especially when compared to the EEG activity.

Mean arterial pressure (MAP) was not different between groups prior to CPB. Immediately after institution of CPB the MAP fell in both groups although not as profoundly in the PFE group (Figure 2).

DISCUSSION

Freeman and Slug reported a high correlation between EEG and cortical blood flow in humans (9,10). Suppression of the EEG during normothermic CPB can be indicative of severe hypoxia, early phase of air embolism, or low cerebral blood flow and hypotension (11,12). The initiation of CPB is a probable cause for all aforementioned incidents; including the sudden change from pulsatile to laminar flow, the massive bolus of crystalloid prime solution with low oxygen content, and the transient drop in arterial pressure can each be cause for this change in electrical activity, not to mention the possibility of micro air introduced at aortic cannulation.

The etiology of the decrease in MAP is not clear. The volume of dilution of blood by CPB prime was equal in both

Table 2. Cerebral blood flow.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>n</th>
<th>PRE CPB</th>
<th>10' CPB</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-lyte 6</td>
<td>0.600±0.015</td>
<td>0.060±0.023</td>
<td>p=0.8432 (a)</td>
<td></td>
</tr>
<tr>
<td>PFE 7</td>
<td>0.743±0.048</td>
<td>1.050±0.065</td>
<td>p&lt;0.0001 (b)</td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>p=0.0091 (c)</td>
<td>p=0.0001 (d)</td>
<td>unpaired t-Test</td>
<td></td>
</tr>
</tbody>
</table>

Blood flow is measured in ml/min/mg of brain tissue
Interpretation: (p<0.01 for statistical significance)

(a) P-lyte group-no change from pre to 10' CPB
(b) PFE group-statistically significant increase in flow from pre to 10' CPB
(c) Pre CPB-statistically significant higher flow in PFE group
(d) 10' CPB-statistically significant higher flow in PFE group
groups. The amount of PFE in the prime was not substantial enough to affect resistance itself but this was not actively measured. The level of decrease in MAP observed in the P-lyte group was 44% whereas the PFE animals decreased 11%. The level of MAP seen in the P-lyte group should still have been within the realm of cerebral autoregulation if it was intact during those first 10 minutes of CPB. Indeed that micro time span has never been studied for cerebral blood flow and autoregulation. Future research should investigate this phenomena with MAP carefully noted.

The etiology of the increase in cerebral blood flow in PFE treated animals is also not clear considering that pump blood flow was constant in both groups. Whether this is due to the smaller molecule size of the perfluorocarbon or to some other mechanism warrants further investigation.

The physical properties of PFE include increased solubility for oxygen, nitrogen and carbon dioxide as compared to plasma and small particle size (0.1 micron) which permits improved perfusion and gas exchange at the level of the microvasculature. These properties enable PFE to passively transport greater volumes of gases than plasma alone and suggest that perfluorocarbons may provide protection against transient ischemia produced by cerebral air emboli, a state of hypoperfusion, or otherwise decreased oxygen content. Previous work using a different PFE demonstrated that there was a protective effect from cerebral air emboli in rabbits when pretreated with PFE (13). Other works have documented that other end organs are also protected from gaseous emboli (14,15).

The perfluorocarbon emulsion used in this study is comprised of pure perfluorocarbon equal to 40% (v/v) of the total emulsion volume. High concentration of the active vehicle is desired in order to transport a significant amount of oxygen; this is because the oxygen dissociation curve is linear for fluorocarbons and a function of both fluorocarbon content and the partial pressure of oxygen. The increase in available oxygen may be responsible for the more rapid and increased recovery of the EEG that we observed at the onset of CPB. The smaller molecule size may be responsible for the increased blood flow.

CONCLUSION

Clinically, with the growing popularity of normothermic CPB and anesthesia techniques that encourage early extubation, this transient depression of the EEG at the onset of bypass can only be magnified. An intraoperative adjunct that is easily incorporated within a CPB protocol and is capable of minimizing or reducing the observed decrease in cerebral electrical activity during the onset of CPB may lead to a decreased incidence of postoperative neurological complications.

The addition of perfluorocarbon to the prime lessens the suppression of EEG at the onset of CPB and decreases the time of recovery to base line power. Cerebral blood flow is increased in animals when the CPB circuit is primed with perfluorocarbon emulsion. We believe the effect of this phenomenon and the effects of perfluorocarbon on it warrant further investigation.

REFERENCES


