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The Effects of Traumatic Brain Injury on Regional Cerebral Blood Flow in Rats

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ABSTRACT

Alterations in cerebral blood flow (CBF) are among the most important secondary pathophysiologic consequences of traumatic brain injury. The present study compared CBF in control rats (n = 20) and in rats that received a calibrated experimental traumatic brain injury (n = 17). The traumatized rats were anesthetized with ketamine (25 mg/kg) and xylazine (10 mg/kg), and prepared for fluid percussion injury (FPI). Twenty-four hours later, the rats were anesthetized with 1% halothane in nitrous oxide–oxygen (70:30) and the left atrium was catheterized via a thoroacotomy. The atrial cannula was used to inject 15 μm radiolabeled microspheres to measure CBF. Following surgery, the concentration of halothane was reduced to 0.5% and the rats were paralyzed with pancuronium bromide (0.1 mg/kg). Thirty minutes later, baseline microsphere determinations were made, and the rats were injured (2.47 ± 0.08 atm). Each rat received additional injections of microspheres at two of the following four times (T): 5, 15, 30, and 60 min after the brain injury. The procedures for the control group rats were the same as described above except that the rats were not subjected to the craniotomy and the FPI. The traumatized group exhibited heterogeneous decreases in CBF following trauma. Global CBF in this group was 78% ($p < 0.01$), 64% ($p < 0.05$), 52% ($p < 0.001$) of those in the control group at T5, 15, 30, and 60, respectively. In rats, the most prominent cerebral circulatory changes following fluid percussion injury were early reductions of CBF and an increasingly heterogeneous CBF pattern. Hemorrhage, edema, and elevated prostagandin levels are mechanisms that may contribute to these changes.

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INTRODUCTION

APPROXIMATELY 500,000 AMERICANS EACH YEAR suffer head injury (Frazee, 1986). Seventy-five percent of patients who die from motor vehicle accidents have traumatic brain injuries (TBI) (Frazee, 1986; Geisler and Salcman, 1987). Neurologic outcome following acute brain trauma is the sum of the primary, irreversible damage and secondary damage due to subsequent events. The assumption underlying therapy following brain injury is that some cells may be reversibly injured and that secondary pathologic events may lead to further damage (Friedman, 1986). Timely application of appropriate treatment could promote the recovery of partially injured cells and prevent secondary damage (Frazee, 1986).

Following TBI, changes in cerebral blood flow (CBF) may contribute to secondary injury. Brain trauma may directly and indirectly injure the cerebral vasculature as well as neural tissue (Nilsson and Nordstrom, 1977; Wei et al., 1980). No data in humans are available to describe changes in CBF immediately following TBI; therefore, such studies have required animal models. Recently a model of TBI has been developed in rats (Dixon et al., 1987) as a modification of the well-characterized feline model of fluid percussion injury (FPI) (Wei et al., 1980, 1982; Dixon et al., 1987; Sullivan et al., 1976; Povlishoch et al., 1978, 1980; Lewelt et al., 1980, 1982; Hayes et al., 1984; Rosner et al., 1984; DeWitt et al., 1986).

The present study was designed to examine alterations in global and regional CBF immediately following FPI in rats.

MATERIALS AND METHODS

Animal Preparation

Male Sprague-Dawley rats (447 ± 39 g, mean ± SD) used in the study were handled in accordance with the guidelines of the Animal Welfare Act (P.L. 89–544) and the Institute of Laboratory Animal Resources (National Research Council) in a protocol approved by the Institutional Animal Care and Use Committee of Bowman Gray School of Medicine. Rats were assigned to control (n = 20) or trauma groups (n = 17).

Traumatized animals underwent a two-stage preparation. Preparation of rats for fluid percussion injury has been described in detail elsewhere (Dixon et al., 1987). Rats were anesthetized with ketamine (25 mg/kg, intramuscularly [IM]) and xylazine (10 mg/kg, IM) and a 5 mm craniotomy was trephined into the calvarium over the superior sagittal sinus. Two stainless steel screws (length 4 mm, tip o.d. 1 mm) were placed in the left parietal bone 4 mm lateral to the bregma and in the occipital bone 2 mm caudal to the lambda, respectively. A modified Luer-Lok syringe hub, 5 mm o.d., was placed over the exposed dura and bonded with dental acrylic poured around the syringe hub and the stainless steel screws. The rats were returned to their cages and allowed to recover for 24 h. The next day, anesthesia was induced using the same anesthetic mixture (ketamine and xylaxine, IM). The animals were intubated and ventilated with a mixture of 1% halothane in 70% nitrous oxide and 30% oxygen using a volume mechanical ventilator (EDCO Scientific Inc.). Rectal temperature was monitored continuously and maintained at 36.5–37.5 °C using a heating pad. The right femoral artery was cannulated for blood pressure monitoring using a quartz transducer (Hewlett Packard) and an eight-channel polygraph (Hewlett Packard 8890A). Arterial blood gases were analyzed using a 1306 pH/blood gas analyzer and a IL282 Co-Oximeter (Instrumentation Laboratory). Pa_{O_2}, Pa_{CO_2}, and pH were maintained within the normal range during the entire experiment by adjusting ventilatory rate and tidal volume, and by administering sodium bicarbonate. A second cannula was placed in the left femoral artery for withdrawal of the reference sample during microsphere injection. Through a left thoracotomy, a left atrial cannulation was performed. The catheter consisted of silastic tubing (0.02 inches, i.d. × 0.037 inches, o.d., Dow Corning) with a 2 mm silicon sleeve 0.5 cm from the tip. The cannula was inserted through a hole punctured in

the wall of the left atrium with a 23 gauge needle, and sutured in the left atrium with a 7–0 silk suture previously sewn through the silicon sleeve of the cannula.

Following surgery, the concentration of halothane was reduced to 0.5% and the rats were paralyzed with pancuronium bromide (0.1 mg/kg). Thirty minutes later, pretrauma (baseline) hemodynamic values were recorded and a baseline injection of radiolabeled microsphere was performed. Fifteen minutes later, the rats were subjected to FPI. Each rat was randomly assigned to receive additional injections of microspheres at two of the following four times (T): 5, 15, 30, and 60 min after head trauma. All animals were killed after T60 by injection of a lethal dose of potassium chloride into the left atrial catheter. The brains were removed, dissected, weighed, and counted in a gamma counter.

The experimental procedures for the control group were the same as described above except that the rats were not subjected to the craniotomy and the FPI.

Fluid Percussion Brain Injury

The FPI device consisted of a Plexiglas cylinder (60 cm long and 4.5 cm in diameter) with a cork-covered piston mounted on O-rings at one end. The other end of the cylinder was fitted with a 2 cm long metal housing on which a transducer was mounted. Fastened to this end was a right angle tube that ended with a male Luer-Lok fitting. This was connected to a female Luer-Lok fitting (a modified Luer-Lok needle hub) that had been implanted over the skull opening. The entire system was filled with 37 °C isotonic saline. The injury was induced by a metal pendulum that struck the piston of the injury device from a predetermined height. The resulting pressure pulse was measured extracranially by the transducer at the time of injury and recorded on a storage oscilloscope. The FPI device transiently injects a constant (depending on level of injury) volume of saline into the closed cranial cavity, thereby producing brief displacement and deformation of brain tissue. The magnitude of the injury is regulated by varying the height of the pendulum. The FPI device has been described in detail elsewhere (Wei et al., 1980; Sullivan et al., 1976).

The magnitude of the injury we used was 2.47 ± 0.08 atm. for the peak pressure and 11.2 ± 0.26 msec for the duration of the insult pulse. The animals were detached from the trauma device immediately after the FPI.

Radioactive Microsphere Technique

Cerebral blood flow was measured using the radioactive microsphere technique (Rudolph and Heymann, 1967). Microspheres (15 μm, DuPont, New England Nuclear Products) labeled with ^{113}Sn, ^{85}Sr, or ^{46}Sc were injected in a rotated sequence. The microspheres suspended in saline with 0.01% Tween 80 were shaken vigorously for 3 min and an aliquot (0.12–0.22 ml) was withdrawn into a length of polyethylene (PE) tubing that was sealed and counted. Immediately preceding injection, the tubing was sonicated for 20 min to maintain even mixing. Before injection, the tubing was opened by cutting the ends, and attached to the left atrial catheter and a 1 ml flush syringe. Approximately 230,000–299,000 spheres were injected into the left atrium over a 15 sec period followed by a 35 sec flush with 1 ml of saline. Beginning 10 sec before the injection and continuing for 30 sec after the flush, a reference arterial blood sample was withdrawn from the left femoral artery at a rate of 0.68 ml/min using a syringe pump (EDCO Scientific Inc). Following the injection, the PE tubing was counted and subtracted from the preinjection count to determine the number of microspheres injected.

At the end of the experiment the rats were killed and the brains were removed and dissected. The hemispheres were divided into left and right halves, which were sectioned into frontal, temporoparietal, and occipital lobes. The cerebellum was removed and the brainstem was sectioned into diencephalon, midbrain, pons, and medulla. Tissue samples were placed in preweighed counting vials, weighed, and counted in an Auto-Gamma 5000 gamma counter (Packard Instru-

ments). Corrections for isotope overlap were performed automatically by a microcomputer connected to the gamma counter. The CBF was calculated using the following equation (Hoffbrand and Forsyth, 1969; Marcus et al., 1976):

$$\text{CBF (ml/100 g/min)} = \frac{C_b \times \text{RBF} \times 100}{C_r \times W_b}$$

C_b = counts/min in brain
C_r = counts/min in reference sample
RBF = arterial withdrawal rate
W_b = weight (g) of tissue sample

Electroencephalographic Recording

Cortical electroencephalograms (EEGs) were sequentially recorded in 13 traumatized rats from bipolar stainless steel screw electrodes implanted in the parietal and occipital bones as described above. The amplifier and polygraph specifications (time constant 0.3 sec, filter position open, paper speed 25 mm/sec, sensitivity 0.2 mv/cm) were kept constant in all experiments. The EEG recordings were analyzed visually. Average EEG amplitudes were calculated at baseline, 5, 15, 30, and 60 min after the trauma, using the area under the corresponding EEG trace, and expressed as a percentage of baseline.

Statistical Analysis

Absolute values were used to compare CBF at baseline between the two groups in individual brain structures. To correct for nonlongitudinal effects and to evaluate better the changes over time following the injury, the values in both groups were expressed as percentage of baseline (pretrauma), and presented as mean ± SEM. A repeated measures analysis of variance was performed on regional CBF of all regions and average EEG amplitude to assess the overall group effect over time after injury or sham injury. Whenever the F ratio was significant, further comparisons were made of the mean between the baseline and any of the four times (5, 15, 30, and 60 min posttrauma), using the least significant difference test. For the intergroup comparison, unpaired Student's t-test with pooled estimate of variance was used. A p value less than 0.05 was regarded as significant.

RESULTS

Physiological Status

There were no significant differences between the control and traumatized groups in body weight, blood gases, or body temperature (Table 1). Fluid percussion injury produced a transient increase in mean arterial blood pressure (from 80 ± 16 to 131 ± 27 mmHg), which peaked in 30 ± 11.5 sec and returned to baseline levels within 367 ± 128 sec after injury. In addition, the hemoglobin concentration was significantly reduced in the traumatized group at T60 ($p < 0.05$ vs baseline).

CBF Changes

Baseline global CBF values, although higher in the traumatized group than in the control group, were not statistically different. The control group exhibited significant increases in global and regional CBF over time (Table 2, Fig. 1). In contrast, the traumatized group exhibited progressive,

TABLE 1. PHYSIOLOGIC PARAMETERS (MEAN ± SEM) IN CONTROL (C, n =20) AND TRAUMATIZED (T, n = 17) RATS.

		Pretrauma	*Posttrauma (min)*			
		(baseline)	*5*	*15*	*30*	*60*
Cardiac output (ml/100g/min)	C	20.9 ± 0.9	19.6 ± 1.8	20.8 ± 1.9	18.6 ± 1.3	18.7 ± 0.9
	T	19.3 ± 1.2	21.9 ± 2.0	21.0 ± 2.1	18.0 ± 2.0	15.1 ± 2.7
Mean arterial pressure (mmHg)	C	74 ± 2	75 ± 5	73 ± 3	75 ± 4	75 ± 5
	T	80 ± 4	83 ± 5	79 ± 8	79 ± 8	65 ± 8
Heart rate (bpm)	C	300 ± 8	321 ± 12	314 ± 12	311 ± 12	307 ± 14
	T	287 ± 6	305 ± 16	334 ± 15	321 ± 18	308 ± 13
pH	C	7.38 ± .01	7.38 ± .01	7.36 ± .01	7.35 ± .01	7.35 ± .01
	T	7.37 ± .01	7.36 ± .01	7.39 ± .01	7.36 ± .01	7.36 ± .01
$Paco_2$ (mmHg)	C	39.4 ± 0.7	38.3 ± 0.9	40.2 ± 1.1	39.9 ± 1.0	37.7 ± 0.8
	T	40.2 ± 0.7	39.8 ± 0.9	40.3 ± 1.0	39.2 ± 1.3	39.4 ± 0.9
Pao_2 (mmHg)	C	94 ± 5	89 ± 6	84 ± 4	89 ± 9	98 ± 13
	T	99 ± 4	98 ± 6	87 ± 4	109 ± 9	104 ± 13
Hemoglobin (g/dl)	C	11.2 ± 0.4	11.0 ± 0.0	10.4 ± 0.3	10.7 ± 0.4	10.5 ± 0.5
	T	11.7 ± 0.4	11.0 ± 0.0	10.2 ± 0.3	9.7 ± 1.8	9.8 ± 0.7
Body weight (g)	C	440 ± 6				
	T	456 ± 12				

TABLE 2. CEREBRAL BLOOD FLOW (MEAN ± SEM) IN CONTROL (C, n = 20) AND TRAUMATIZED (T, n = 17) RATS.

		Baseline (ml/100g/min)	*Posttrauma (min) (percentage of baseline)*			
			5	*15*	*30*	*60*
Whole brain	C	112.3 ± 6.3	117 ± 5	121 ± 5[a]	137 ± 9[b]	162 ± 11[b]
	T	132.3 ± 8.4	91 ± 7[c]	78 ± 18[d]	71 ± 11[c]	65 ± 18[c]
Cerebral hemispheres	C	119.5 ± 6.6	115 ± 4	117 ± 6	136 ± 9[b]	158 ± 12[b]
	T	148.2 ± 10.2[d]	86 ± 7[c]	74 ± 19[d]	63 ± 11[a,c]	57 ± 17[a,c]
Brainstem	C	95.5 ± 6.1	120 ± 5[b]	126 ± 6[b]	138 ± 8[b]	174 ± 12[b]
	T	113.5 ± 6.6	92 ± 10[d]	84 ± 16[d]	83 ± 12[a,c]	80 ± 21[c]
Cerebellum	C	114.4 ± 7.0	120 ± 7	131 ± 6[a]	145 ± 13[b]	176 ± 13[b]
	T	118.6 ± 6.7	103 ± 10	87 ± 16[d]	86 ± 15[c]	82 ± 23[c]

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] Intergroup comparison (control vs. trauma): $p < 0.01$.
[d] Intergroup comparison (control vs. trauma): $p < 0.05$.

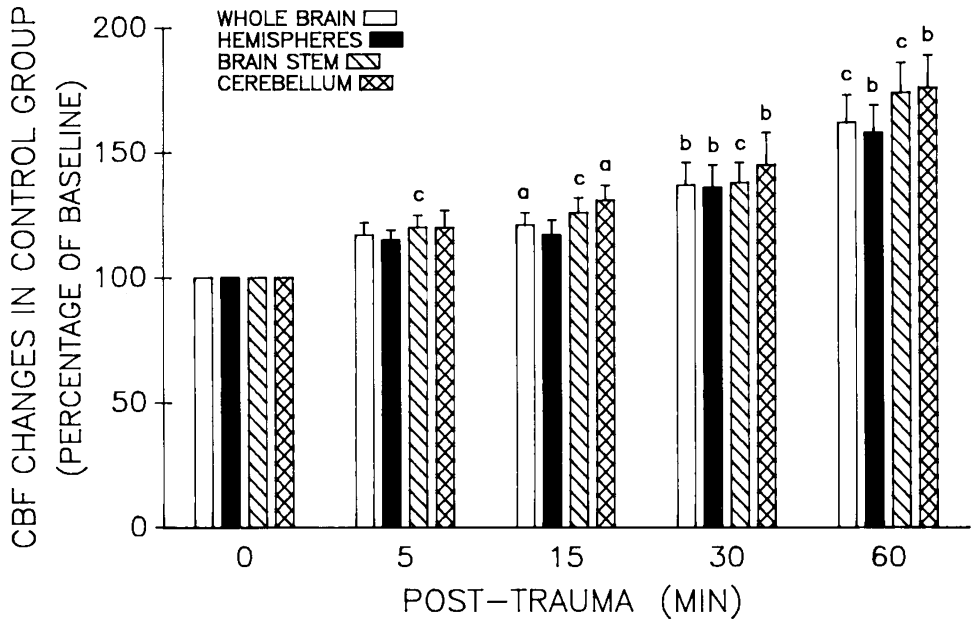

FIG. 1. Cerebral blood flow changes over time in the control (uninjured) group. Values are expressed as mean ± SEM percentage of baseline CBF value. Statistical comparisons are relative to baseline CBF value. a, $p < 0.05$; b, $p < 0.01$; c, $p < 0.001$; $n = 20$.

heterogeneous decreases in global and regional CBF with time (Table 2, Fig. 2). The global CBF in this group was 78% ($p < 0.01$), 64% ($p < 0.05$), 52% ($p < 0.001$), and 40% ($p < 0.001$), of those in the control group at T5, 15, 30, and 60, respectively (Fig. 3). Cerebral blood flow tended to decline less in the brainstem and cerebellum than in the hemispheres.

EEG Changes

There was an immediate diminution and flattening of EEG activity following FPI. Significant ($p < 0.05$) posttraumatic decreases in average EEG amplitude persisted throughout the entire 60 min observation period (Fig. 4).

Gross Pathologic Changes

Gross examination of the brain was performed following each experiment. Brains from the control group appeared normal, without hemorrhage or other abnormalities. In the traumatized group, there was evidence of epidural, subdural, and intraparenchymal hemorrhage. Epidural hemorrhage was observed over both the dorsal and ventral surfaces of the brain. Intraparenchymal petechial hemorrhages were observed in the cerebral cortex (primarily in the parietal lobe) and in the brainstem (primarily in the rostral part). The weights (mean ± SEM) of the whole brain, hemispheres, brainstem, and cerebellum in traumatized and control groups were 2292.0 ± 24.6 mg vs. 2198.1 ± 24.0 mg ($p < 0.01$); 1196.6 ± 11.8 mg vs. 1189.4 ± 16.5 mg; 671.5 ± 13.6 mg vs. 631.4 ± 12.5 mg ($p < 0.02$); and 332.8 ± 4.5 mg vs. 322.1 ± 4.6 mg ($p = 0.054$), respectively.

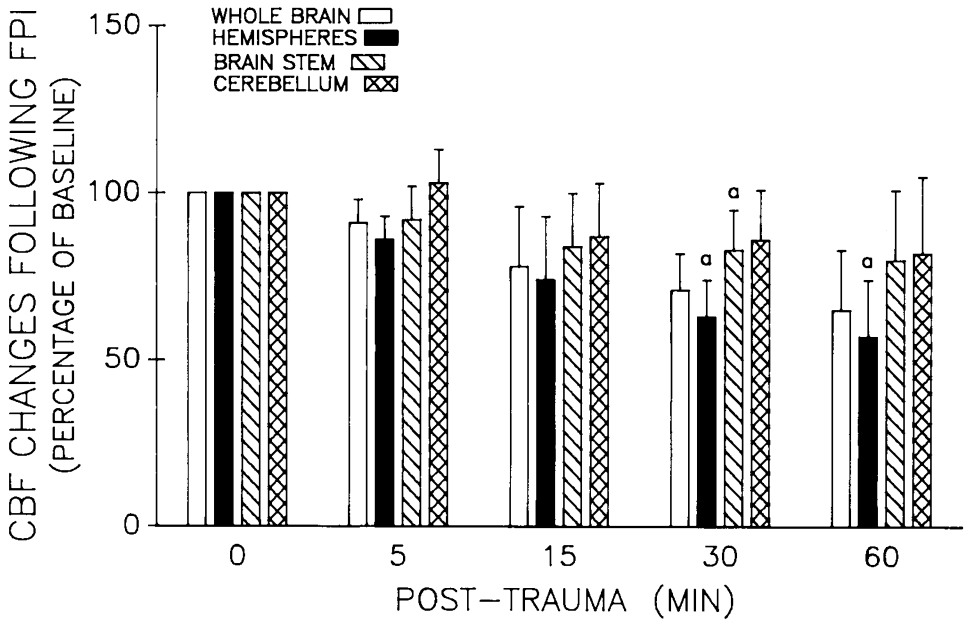

FIG. 2. Cerebral blood flow changes over time after fluid percussion injury (FPI, 2.47 ± 0.08 atm). Values are expressed as mean ± SEM percentage of baseline (preinjury) CBF value. Statistical comparisons are relative to preinjury CBF value. .a, $p < 0.05$; $n = 17$.

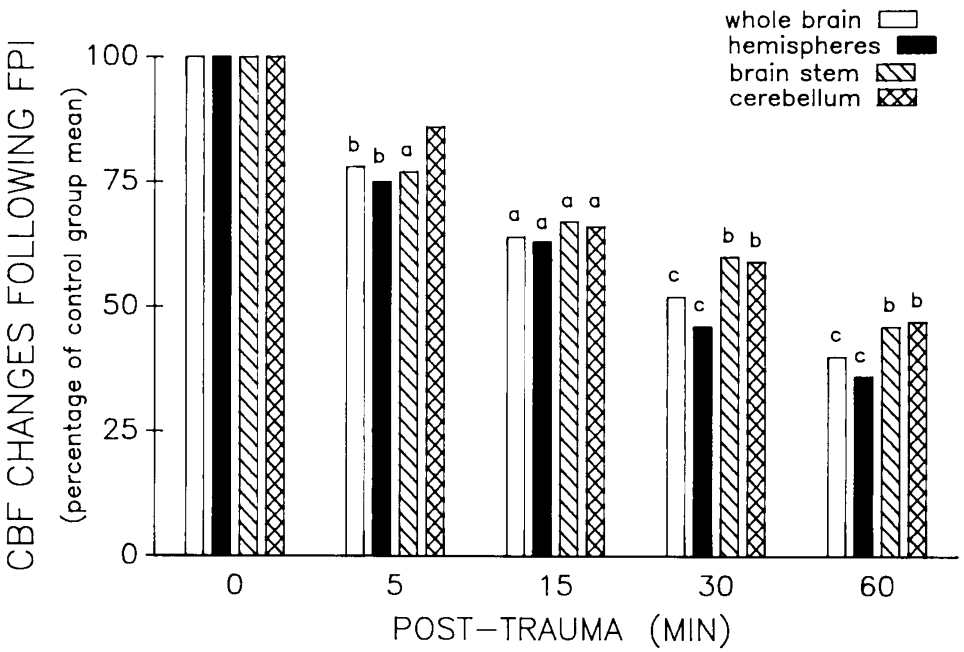

FIG. 3. Cerebral blood flow changes over time after fluid percussion injury (FPI, 2.47 ± 0.08 atm). Values are expressed as percentage of CBF values in uninjured group for each brain region and time. Statistical comparisons were made between mean values for control and injured groups. a, $p < 0.05$; b, $p < 0.01$; c, $p < 0.001$.

DISCUSSION

The present study demonstrated that FPI in rats produces significant decreases in local CBF, even in the presence of a potent vasodilatory anesthetic.

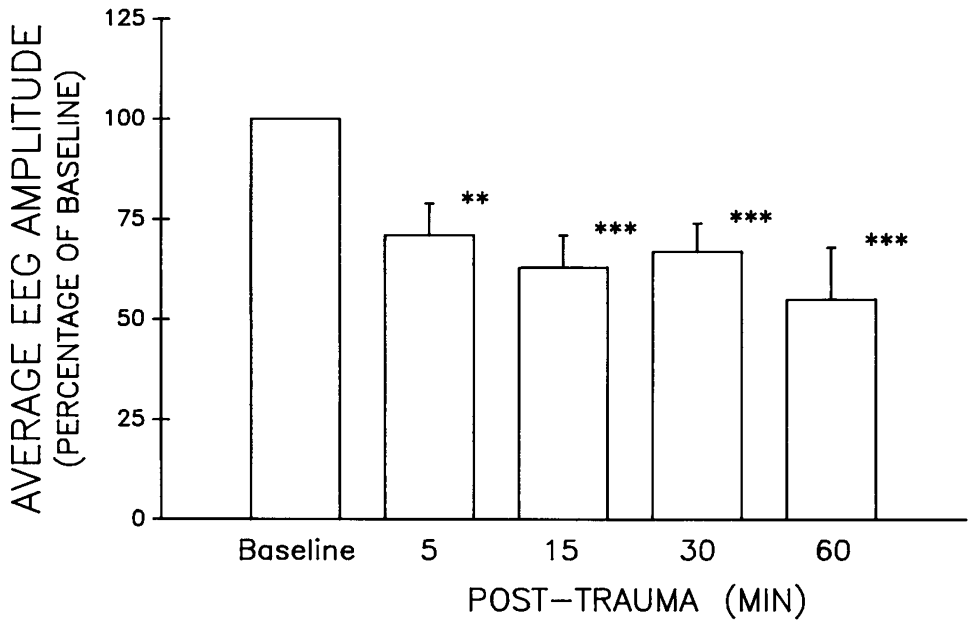

FIG. 4. Changes in averaged EEG amplitude over time after fluid percussion injury (FPI, 2.47 ± 0.08 atm). Values are expressed as mean ± SEM percent of preinjury (0) values. b, $p < 0.01$; *c*, $p < 0.001$; $n = 17$.

Fluid Percussion Injury Model

The FPI model produces a pressure pulse that is recorded extracranially. The pressure pulse causes direct compression of the exposed brain, permitting study of the effects of the force dissipated in the brain itself without the confounding influence of force dissipated in contiguous structures. The injury can be precisely quantitated as a simple pressure impulse, which represents the energy dissipated in the brain (Sullivan et al., 1976). The impulse is the product of the force and the time over which it acts. As the level of injury is increased, only the force of the impact increases, while the duration and waveform remain constant (Sullivan et al., 1976). Therefore, the physiologic response to trauma is the function of a single variable: the peak pressure. Fluid percussion injury produces an "elongation" of the brain, forcing the brainstem towards the foramen magnum (Lindgren and Rinder, 1969; Rinder and Olsson, 1968). This deformation is considered to be similar to that occurring in human closed head injury (Lindgren and Rinder, 1969; Rinder and Olsson, 1968). The midbrain is thought to be a critical focus of traumatic brain injury (Thompson and Salcman, 1988), and this model reproduces many of the major features of human brain injury.

Blood Pressure Response

Fluid percussion injury results in a massive catecholamine release (Rosner et al., 1984), which is likely to be responsible for the hypertensive response to the injury (Clifton et al., 1981, 1983). The cardiopulmonary effects of the catecholamine release after FPI correlate with the intensity of the injury up to 2.5–3.0 atm (Rosner et al., 1984). In our experiments, the injury level was constant (2.47 ± 0.08 atm). The posttraumatic hypertensive response in our traumatized rats was comparable in magnitude and duration to hypertensive responses reported by Dixon et al. (1987) and Lyeth et al. (1988) in similarily injured rats.

Radioactive Microsphere Technique

The radiolabeled microsphere technique has been extensively used for the determination of the regional CBF (rCBF) in large mammals (DeWitt et al., 1986; Rudolph and Heymann, 1967; Hoffbrand and Forsyth, 1969; Marcus et al., 1976; Alm, 1975; Heymann et al., 1977). Microspheres have also been used to measure rCBF in rats (Horton et al., 1980; Malik et al., 1976; Sasaki and Wagner, 1971; Stanek et al., 1983; Yamakami et al., 1989). Most of these studies were performed using a single left ventricular injection; two studies used a left atrial approach (Stanek et al., 1983; Yamakami et al., 1989), which produces better mixing (Buckberg et al., 1971). The present study confirms that repeated left atrial injections of microspheres are feasible for CBF determinations in rats. However, despite its feasibility, this technique requires considerable surgical preparation (i.e., thoracotomy, left atrial catheterization, cannulations of both femoral arteries, multiple blood gas samplings, and arterial reference sampling).

The precision of the microsphere method is dependent upon the number of microspheres in the reference and tissue samples (Buckberg et al., 1971; Dole et al., 1982). Buckberg et al., (1971) calculated theoretically, and confirmed experimentally, that errors due to nonrandom sphere distribution were minimized if at least 400 spheres were present in each tissue and reference sample. We injected approximately 250,000 microspheres for each CBF measurement. Direct determination of microsphere numbers in the present studies indicated that there were at least 2,000 beads in each reference sample and at least 400 microspheres in each brain region. The injection of the microspheres and the withdrawal of the reference samples resulted in minimal changes in monitored hemodynamic parameters. Both absolute and percentage changes indicated that mixing was adequate since there were no systematic left vs. right differences for paired brain structures in the control group throughout the entire time course or in the traumatized group at the baseline.

CBF Changes

Halothane is the most potent cerebral vasodilator among the volatile anesthetic agents (Shapiro, 1986). In rabbits, 0.5% halothane in 70% nitrous oxide–30% oxygen is associated with a steady increase in CBF over almost 4 h (Devalois and Peperkamp, 1972). These data are consistent with our results in the control group. Therefore, we believe that the increase in CBF in the control group was related to the anesthetic used.

Consistent with the observations of Yamakami et al. (1987, 1989), FPI caused an immediate and marked reduction of CBF in all brain regions. Hemispheric CBF decreased more than CBF in brainstem and cerebellum. Regional CBF was also reduced heterogeneously among paired brain regions in individual animals. In the control group at all time intervals and in the traumatized group at baseline, most CBF differences between paired regions were less than 5%. Following FPI, the difference between paired regions increased, with most exceeding 20% and some as great as 50%. The increased heterogeneity, resulting from increased asymmetry, appears to represent a pathophysiologic consequence of FPI.

A number of processes may contribute to reduced CBF following TBI. The hemorrhage that occurred following FPI may have exerted a mass effect that increased intracranial pressure (ICP) and decreased cerebral perfusion pressure. Studies in rodents have shown that blood in the subarachnoid space induces vasospasm and decreases CBF acutely (Delgado et al., 1986) or progressively over 60 min (Solomon et al., 1985). The brainstem may play a role in the development of cerebral vasospasm following subarachnoid hemorrhage (Svendgaard et al., 1985) and local vascular spasm may contribute to regional heterogeneity (Marovitch et al., 1983).

There is evidence that increased permeability of cerebral capillaries accompanies acute brain injury and causes cerebral edema (Seelig and Marshall, 1985). Consistent with this are our observations that all brain structures in the traumatized group were significantly heavier than those in the control group. Since ICP, brain water content and pial vessel diameter were not measured

in our study, it is difficult to determine the contributions of these mechanisms in posttraumatic hypoperfusion.

Prostaglandin-induced global or regional changes in cerebral vascular resistance (CVR) and CBF may be involved in the control of CBF in both physiologic and pathologic conditions (Kontos et al, 1981; Wolfe, 1979). A variety of insults including trauma, ischemia (Prough et al, 1986; Dempsey et al, 1986), acute hypertension Shohami et al., 1987, 1988), (Ment et al., 1986), and seizure (Birkle and Bazan, 1987); reportedly result in cerebral phospholipid degradation and the release of arachidonic acid and prostaglandins (PGs). Shohami et al. (1987) demonstrated increases in rates of PGE_2, thromboxane B_2 (TxB_2), and 6-keto-$PGF_{1\alpha}$ (the stable metabolites of thromboxane A_2 and PGI_2, respectively) synthesis in the brain in rats subjected to a weight drop brain injury. Large increases in brain tissue levels of prostaglandin E_2 and TxB_2 increase markedly following FPI in rats (Dewitt et al., 1987). Thromboxane is a potent constrictor of both systemic (Altura and Altura, 1976) and cerebral (Ellis et al., 1977) vascular smooth muscle. Following cerebral ischemia, elevated PG levels are associated with secondary decreases in CBF (Prough et al., 1986; Dempsey et al., 1986). Inhibition of PG synthesis improves postischemia cerebral perfusion in some (Gnce et al., 1987; Kochanek et al., 1987) but not all situations (Prough et al., 1986; Moufarrij et al., 1984). These data suggest that elevated TxA_2 levels may contribute to the decreased CBF after TBI in rats reported here and elsewhere (Yamakami et al., 1987, 1989; Yuan et al., 1988; DeWitt et al., 1988). Elevations of PG levels were more prominent in the hemispheres than in the brainstem (DeWitt et al., 1987). This may explain, in part, why CBF declined more in the hemispheres than in the brainstem.

We observed a consistent reduction in EEG activity immediately following FPI. Cerebral blood flow did not decrease to levels that have been reported to suppress EEG activity (Gregory et al., 1979), which suggests that neuronal activity may have been directly affected by the mechanical insult. Spreading cortical depression produces decreases in EEG amplitude (Leao, 1944) and spreading depression has been reported to occur following traumatic brain injury in rats (Sumami et al., 1987; DeWitt, unpublished observations). Spreading depression produces decreases in CBF that persist for at least 60 min (Lauritzen et al., 1982). Therefore, posttraumatic spreading depression may contribute to the decreases in EEG amplitude and CBF levels. It is unlikely that spreading depression is entirely responsible for changes in CBF or EEG, since the decreases in CBF following spreading depression are of a lower magnitude (Lauritzen et al., 1982) than we observed in the present study and postspreading depression EEG changes have been reported to resolve within 15 min (Gregory et al., 1979).

The present study demonstrated that moderate FPI caused significant, heterogeneous decreases in global and regional CBF and in EEG amplitude. These changes persisted for the 60 min experimental period. While we cannot exclude the possibility that posttraumatic hypoperfusion is due to elevated ICP or vasospasm, other investigations in our laboratory (DeWitt et al., 1987) and others (Shohami et al., 1987) suggest that the trauma-induced increases in PG levels may explain these changes.

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