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CARDIAC ARRHYTHMIAS RESULTING FROM EXPERIMENTAL HEAD INJURY.(U)
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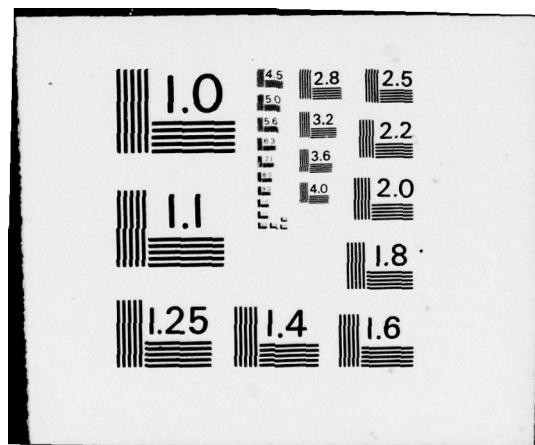
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The cardiovascular events resulting from experimental head injury were studied to determine the incidence of cardiac arrhythmias and to define the autonomic mechanisms responsible for these changes. The electrocardiogram and arterial blood pressure were recorded in anesthetized monkeys before and after the animals were subjected to temporoparietal head impact. Cardiac arrhythmias and hypotension occurred immediately following impact in every animal studied. Various A-V		

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nodal and ventricular arrhythmias were seen. Cholinergic blockade was found to prevent arrhythmias induced by head injury whereas adrenergic blockade was found to be ineffective. These results suggest that in human head injury, the cardiovascular events alone may be life-threatening. Since head trauma is a common cause of injury and death of military personnel in both combat and peacetime situations, early evaluation of the cardiovascular status of the head injured patient should be stressed.

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INTRODUCTION

Since 1934 a number of clinical reports have described the occurrence of cardiac arrhythmias following head injury.^{1,4,8} In the first systematic study of this phenomenon, Hersch⁴ reported that in a series of 164 patients admitted with head injury, 31 percent exhibited some form of cardiac arrhythmia. In a more recent study VanderArk¹³ observed cardiac arrhythmias in 41 of 100 consecutive patients with acute subdural hematoma, the majority of these cases resulting from traumatic injury. The potential seriousness of these arrhythmias is reflected by the observation that greater than half of them were ventricular arrhythmias ranging in severity from premature ventricular contractions to ventricular tachycardia and ventricular fibrillation.

Experimental studies have also demonstrated cardiac arrhythmias following head injuries in mice,⁵ dogs,² and monkeys.^{3,6,9} However, the variations in species, anesthesia, site and force of impact, and physiological status of the animals render the various results difficult to assess.

Thus both clinical and experimental studies have demonstrated cardiac arrhythmias following head injury. Yet the significance of the cardiovascular changes after head injury and the mechanisms responsible for them remain poorly understood. The purpose of the present study was to explore systematically the cardiovascular changes resulting from head injury in the primate while paying particular attention to such variables as site and force of impact, anesthesia and physiological status of the animals. A further goal of this study was to determine the autonomic mechanisms responsible for the cardiovascular changes observed.

METHODS

Twenty-four Macaca mulatta monkeys unselected as to sex and weighing 2.5 to 4.0 kg were used for these experiments. Anesthesia was induced by a single intravenous injection of thiopental sodium (20 mg/kg) following which the animals were intubated and ventilated with a gas mixture of nitrous oxide

(50-75 percent), oxygen (24-50 percent) and halothane (0.75-1.0 percent). The femoral artery and vein were catheterized to record blood pressure and administer drugs. Arterial blood gas measurements were made throughout the experiment and ventilation was adjusted to maintain PCO_2 , PO_2 and pH within normal physiological ranges. The electrocardiogram (Lead II) and arterial blood pressure were recorded continuously.

In preparation for impact the animals were seated and restrained in a chair mounted on an acceleration sled. Details of the acceleration and impacting device have been previously reported.^{11,12} Head movement was restricted by a fin attached to the skull and a guide rail system which allowed free movement of the head only in the impact plane. After completing all surgical procedures and approximately 30 minutes before impact, halothane administration was discontinued and anesthesia was maintained with nitrous oxide and oxygen. Small doses of succinylcholine (1.0 mg, iv) were given to prevent the possibility of head movement prior to impact. The animals were accelerated along a 15-foot track in a chair drawn by the force of a falling 40-kg weight. The temporoparietal skull area struck a fixed impactor which had a circular impact area of 4.9 cm². Force of impact was measured by using a load cell mounted in series with the impactor. Impact forces of 400 to 1000 lbs were recorded with impulse durations of 3 to 6 msec.

The animals were studied for approximately 30 minutes after impact during which time anesthesia was maintained with nitrous oxide and oxygen. Blood gas measurements were made within the 1st minute after impact to insure that cardiovascular changes were not the result of hypoxia. At the termination of the experiments animals were euthanatized by administration of a lethal dose of pentobarbital.

Animals were divided into four experimental groups. In the first group there was no pharmacological intervention prior to head injury. Animals in each of the other three groups were pretreated with either atropine, propranolol, or phentolamine.

RESULTS

Cardiac arrhythmias occurred immediately following temporoparietal impact in each of 10 animals studied. Various arrhythmias occurred including A-V nodal rhythm, A-V dissociation, and multifocal nodal and ventricular rhythms. Records from two experiments are shown in Figures 1 and 2. In the first example it can be seen that impact resulted in abrupt cessation of sinus rhythm and emergence of a slow nodal rhythm. Sinus rhythm returned within 75 seconds after impact. In the second example (Figure 2) nodal bradycardia occurred immediately after impact, but by 90 seconds postimpact a multifocal

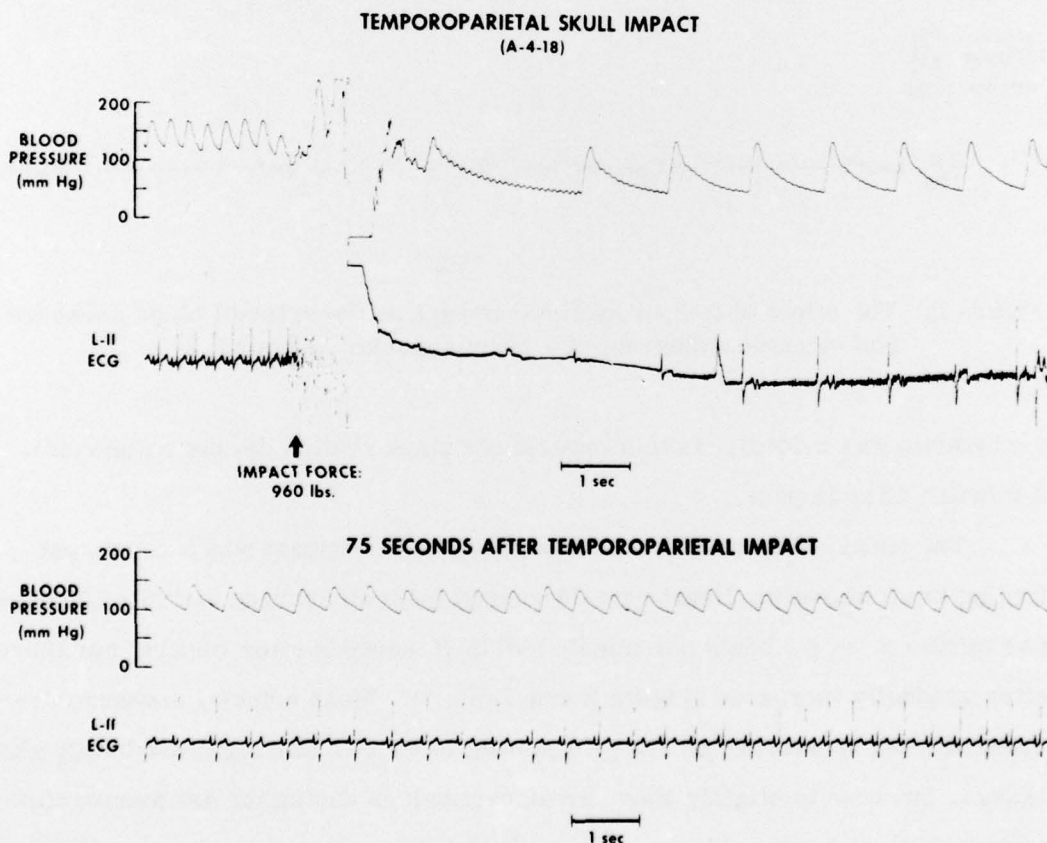


Figure 1. The effect of temporoparietal impact on the arterial blood pressure and electrocardiogram of a rhesus monkey (example 1)

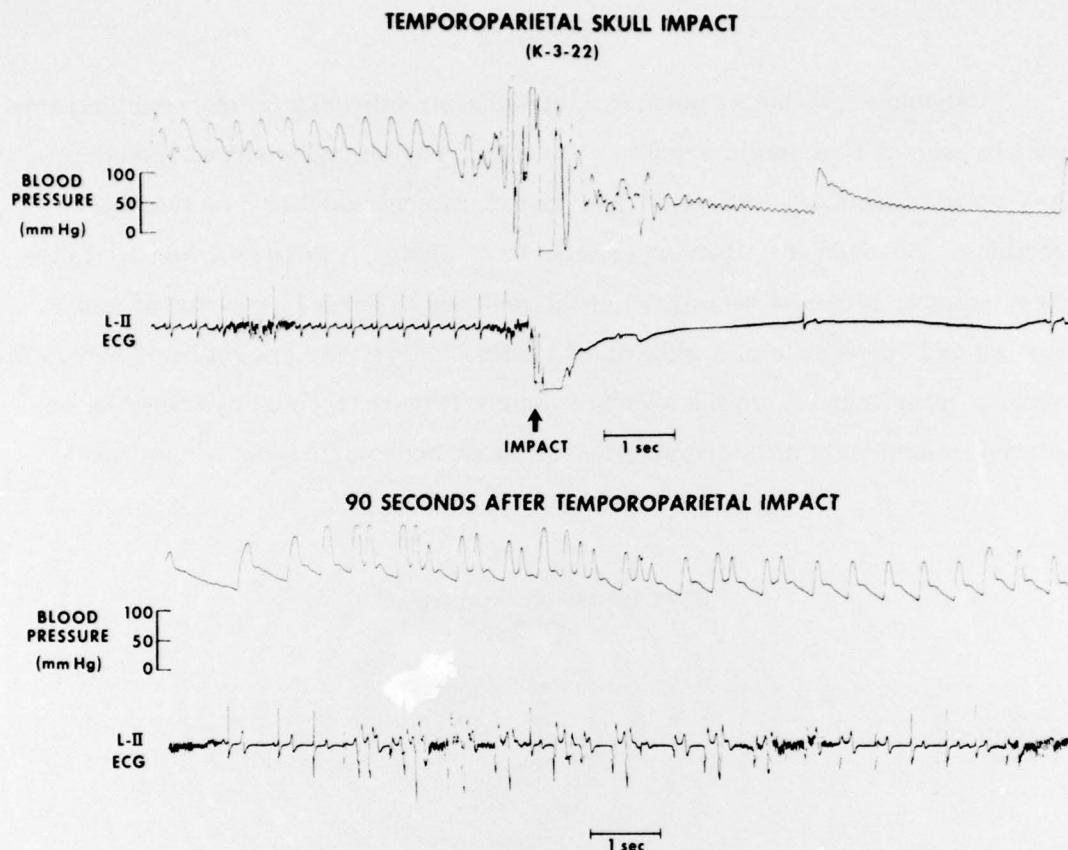


Figure 2. The effect of temporoparietal impact on the arterial blood pressure and electrocardiogram of a rhesus monkey (example 2)

arrhythmia was evident. In this experiment sinus rhythm did not return until 2 minutes after impact.

The nodal bradycardia seen immediately after impact was a consistent finding in all animals. Heart rate decreased from an average of 188 ± 10 beats per minute to 38 ± 8 beats per minute within 10 seconds after impact, and thereafter gradually increased (Figure 3 and Table 1). Mean arterial pressure decreased from an average of 110 ± 10 mm Hg to 68 ± 12 mm Hg immediately after impact, but rose to slightly above preimpact values during the 1st minute after impact (Figure 4 and Table 1). The arrhythmias persisted for an average of

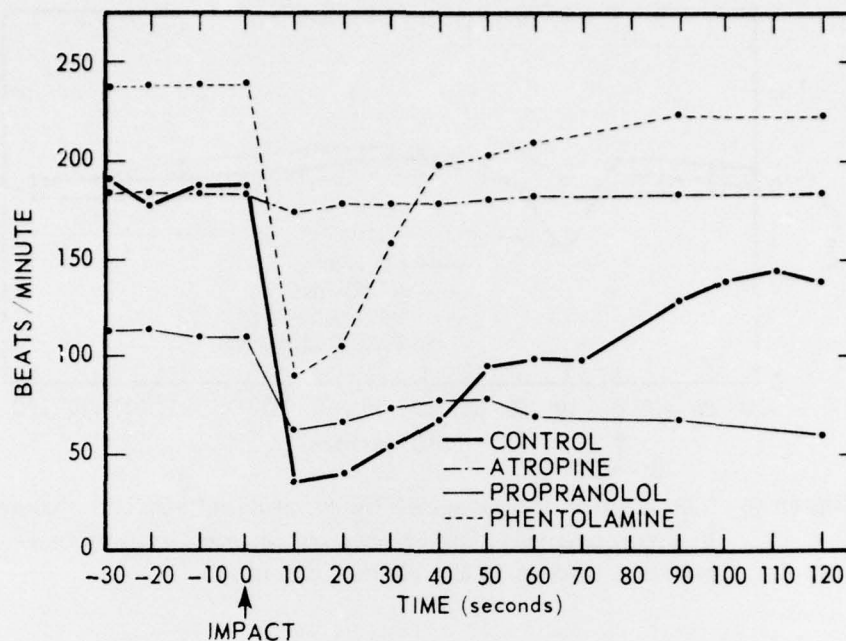


Figure 3. The effects of autonomic blocking agents on the changes in heart rate induced by temporoparietal impact in the rhesus monkey

Table 1. The Effects of Autonomic Blocking Agents on the Changes in Heart Rate and Mean Arterial Blood Pressure Induced by Temporoparietal Impact in the Rhesus Monkey. All values given are mean $\pm$ standard error. The number of animals in each group is indicated.

GROUP		PREIMPACT (SECONDS)			POSTIMPACT (SECONDS)							
		30	20	10	10	20	30	40	50	60	90	120
CONTROL (n=10)	HR	193 $\pm$ 9	182 $\pm$ 15	188 $\pm$ 10	38 $\pm$ 8	43 $\pm$ 9	56 $\pm$ 6	68 $\pm$ 10	96 $\pm$ 19	98 $\pm$ 18	128 $\pm$ 16	139 $\pm$ 16
	BP	110 $\pm$ 10	114 $\pm$ 9	115 $\pm$ 10	68 $\pm$ 12	103 $\pm$ 11	111 $\pm$ 12	117 $\pm$ 10	116 $\pm$ 11	112 $\pm$ 11	106 $\pm$ 12	105 $\pm$ 10
ATROPINE (n=5)	HR	186 $\pm$ 13	185 $\pm$ 13	184 $\pm$ 11	174 $\pm$ 12	178 $\pm$ 13	177 $\pm$ 12	179 $\pm$ 13	182 $\pm$ 13	185 $\pm$ 14	185 $\pm$ 14	185 $\pm$ 13
	BP	100 $\pm$ 15	100 $\pm$ 15	102 $\pm$ 16	104 $\pm$ 11	119 $\pm$ 11	115 $\pm$ 14	109 $\pm$ 13	108 $\pm$ 14	106 $\pm$ 14	95 $\pm$ 13	95 $\pm$ 14
PROPRANOLOL (n=4)	HR	115 $\pm$ 11	115 $\pm$ 11	110 $\pm$ 9	63 $\pm$ 31	68 $\pm$ 33	74 $\pm$ 31	77 $\pm$ 27	78 $\pm$ 25	59 $\pm$ 20	68 $\pm$ 15	60 $\pm$ 5
	BP	103 $\pm$ 9	104 $\pm$ 9	108 $\pm$ 9	93 $\pm$ 37	102 $\pm$ 45	115 $\pm$ 40	120 $\pm$ 37	117 $\pm$ 27	121 $\pm$ 26	114 $\pm$ 18	105 $\pm$ 11
PHENTOLAMINE (n=5)	HR	240 $\pm$ 6	240 $\pm$ 6	240 $\pm$ 6	91 $\pm$ 19	105 $\pm$ 21	158 $\pm$ 26	198 $\pm$ 25	205 $\pm$ 25	210 $\pm$ 22	225 $\pm$ 9	225 $\pm$ 7
	BP	106 $\pm$ 13	106 $\pm$ 13	105 $\pm$ 13	70 $\pm$ 11	75 $\pm$ 13	79 $\pm$ 18	79 $\pm$ 20	78 $\pm$ 19	78 $\pm$ 19	79 $\pm$ 16	78 $\pm$ 18

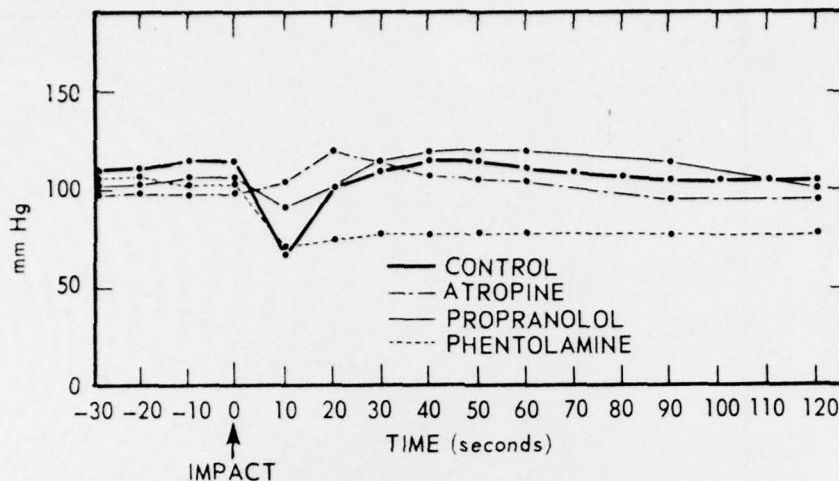


Figure 4. The effects of autonomic blocking agents on the changes in mean arterial blood pressure induced by temporoparietal impact in the rhesus monkey

2 minutes; however, there was considerable variation in duration as can be noted from the examples shown in Figures 1 and 2.

The abrupt decrease in heart rate following impact suggested that the arrhythmias were mediated by the parasympathetic nervous system. To test this hypothesis five animals were subjected to impact after pretreatment with atropine (0.2 mg/kg). Vagal blockade prevented arrhythmias from occurring after temporoparietal impact in each animal tested. Atropine administration did not alter the preimpact heart rates but prevented any significant change in heart rate following impact (Figure 3 and Table 1). Atropine prevented the decrease in mean arterial pressure immediately after impact but did not alter the slight elevation occurring thereafter (Figure 4 and Table 1).

To determine if the sympathetic nervous system was also involved in the generation of these arrhythmias, separate groups of animals were pretreated with alpha- and beta-adrenergic blocking agents before impact. Administration of propranolol (1.0 mg/kg) to four animals failed to prevent arrhythmias from occurring immediately after impact. Propranolol did not prevent a significant decrease in heart rate immediately after impact but prevented the gradual

recovery of heart rate seen in the control group (Figure 3 and Table 1). Impact-induced changes in blood pressure after propranolol were similar to the changes seen in the control group (Figure 4 and Table 1).

In a group of five animals pretreated with phentolamine (2.0 mg/kg), arrhythmias occurred after impact in two animals and failed to occur in three animals. Animals pretreated with phentolamine had a significantly higher base-line heart rate than control animals but exhibited the same degree of bradycardia following impact. In each group heart rate decreased approximately 150 beats per minute immediately after impact (Table 1). The pattern of recovery of heart rate was similar to that seen in the control group (Figure 3). Phentolamine did not prevent the decrease in mean arterial pressure immediately after impact but did prevent the subsequent elevation of blood pressure seen in the other three groups (Figure 4 and Table 1).

DISCUSSION

The results of this study indicate that cardiac arrhythmias consistently occur in the primate following temporoparietal impact, and that these arrhythmias are primarily vagal in origin. Arrhythmias occurred in 10 out of 10 untreated animals subjected to impact whereas in five animals pretreated with atropine, cardiac arrhythmias did not occur.

Beta-adrenergic blockade failed to prevent arrhythmias from occurring after temporoparietal impact. This result suggests that sympathetic influences on the heart were not necessary for the generation of arrhythmias. Alpha-adrenergic blockade prevented arrhythmias from occurring in three animals while it failed to prevent arrhythmias in two animals. Rather than implicating an alpha-adrenergic mechanism in the etiology of impact-induced arrhythmias, we believe that arrhythmias failed to occur only because preimpact heart rates were so markedly elevated. Preimpact heart rates in the five animals treated with phentolamine were 250, 242, 250, 235 and 220. In the three animals with heart rates above 240, temporoparietal impact resulted in sinus bradycardia but

not emergence of an A-V nodal pacemaker. In the two animals with preimpact heart rates of 235 and 220 respectively impact resulted in bradycardia and emergence of an A-V nodal rhythm. Since the mean decrease in heart rate induced by impact was the same in the control group as in the phentolamine treated group (Table 1), it appears that phentolamine did not decrease the parasympathetic hyperactivity induced by impact. However, in the case of animals with high initial heart rates, the vagal hyperactivity induced by impact did not lower heart rate to levels at which nodal pacemakers would become dominant.

Alpha- and beta-adrenergic blockade did produce changes in recovery of heart rate and blood pressure which indicated increased sympathetic activity during the recovery period. For example phentolamine prevented the elevation of blood pressure during the first 2 minutes after impact and propranolol prevented the recovery of heart rate during this period (Figures 3 and 4). These results indicate that in untreated animals subjected to temporoparietal impact, the recovery of heart rate and blood pressure was dependent on sympathetic activation. This also suggests that arrhythmias occurring after the initial nodal bradycardia, such as those occurring 90 seconds after impact in Figure 2, may be the result of sympathetic activation. In the example shown in Figure 2, it appears that the arrhythmia may be the result of simultaneous activation of the parasympathetic and sympathetic nervous systems. Indicative of this is the observation that sinus rate at 90 seconds postimpact was slower than the preimpact heart rate but was interrupted by several volleys of premature beats initiated by faster nodal or ventricular pacemakers. It is known that simultaneous activation of the sympathetic and parasympathetic nervous systems provides a greater arrhythmogenic stimulus than activation of either autonomic division alone.⁶

In summary our results indicate that the initial arrhythmias seen after temporoparietal impact were solely vagal in origin but that later arrhythmias could have resulted from simultaneous sympathetic and parasympathetic activation.

Other investigators have also observed cardiac arrhythmias in monkeys after head injury. Ommaya⁹ first noted arrhythmias and changes in blood pressure in a series of 38 rhesus monkeys subjected to occipital impacts of graded severity. Although only 50 percent of these animals developed arrhythmias, Ommaya made the observation that animals exhibiting electrocardiographic changes invariably died within 24 hours and that no animals died without developing cardiovascular changes immediately after impact.

Fernando et al.³ studied the electrocardiographic changes in stump-tailed monkeys subjected to occipital impacts. Bradycardia consistently occurred after impact, but loss of sinus rhythm occurred in only 5 of 13 animals. In a more recent report McLaurin and Scott⁷ described the results of a similar study in which cardiovascular changes were observed in rhesus monkeys after a blow to the temporal region. Bradycardia consistently occurred after impact, but arrhythmias occurred in only 5 of 11 animals.

The primary difference between results of previous studies and our results is the incidence of arrhythmias seen after head injury. In each of the previous studies arrhythmias were seen in fewer than 50 percent of the animals subjected to head injury whereas in the present study arrhythmias occurred in all untreated animals subjected to temporoparietal impact. We believe these differences are due primarily to differences in anesthetic technique and differences in site and force of impact employed. Both Ommaya⁹ and Fernando et al.³ used barbiturate anesthesia although both authors indicated that animals were only lightly anesthetized at the time of impact. However we have found that even small amounts of pentobarbital can depress autonomic nerve activity and prevent arrhythmias induced by electrical stimulation of the brain (Evans et al., unpublished observations). McLaurin and Scott⁷ used phencyclidine anesthesia, which has been reported to have long lasting central nervous system and cardiovascular effects,¹⁰ but whether these effects could be responsible for the low incidence of arrhythmias is unclear. In the present study monkeys were anesthetized only with nitrous oxide at the time of impact.

Another factor which may account for the differences in incidence of arrhythmias is the force and site of impacts used to produce head injury. Ommaya⁹ and Fernando et al.³ impacted the occipital area whereas we, as well as McLaurin and Scott,⁷ impacted the temporal area. Although we recorded a considerable range of impact forces, arrhythmias consistently occurred even at the lower impact levels. Since McLaurin and Scott⁷ did not measure impact forces, it is not possible to determine whether this factor might account for the lower incidence of arrhythmias reported.

With regard to the clinical implications of the present study several points can be considered. The fact that vagally mediated arrhythmias consistently occurred in the monkey suggests that similar arrhythmias may be a common occurrence in cases of human head injury. Although the arrhythmias seen in the present study were transitory, one would expect the effects of intensive parasympathetic or sympathetic activation to have more serious consequences in patients with preexisting heart disease. Furthermore, in human head injury the cardiovascular effects of excessive autonomic hyperactivity may be complicated by hypoxia resulting from CNS depression or airway obstruction associated with the injury. These considerations raise the possibility that in human head injury the cardiovascular events alone may be life-threatening. This suggests the need for careful and continued evaluation of the cardiovascular status of the head injured patient.

REFERENCES

1. Bramwell, C. Can a head injury cause auricular fibrillation? *Lancet* 1:8-9, 1934.
2. Eichbaum, F. W. and Bissetti, P. C. Cardiovascular reactions to head injury and to acute increase of intracranial pressure. In: *Proceedings of the Third International Congress of Neurological Surgery of the World Federation of Neurosurgical Societies, Copenhagen-Denmark, August 1965*, de Vet, A. C., editor, pp. 160-164. Amsterdam, Excerpta Medica Foundation, 1966.
3. Fernando, O. U., Mariano, G. T., Jr., Gurdjian, E. S. and Hodgson, V. R. Electrocardiographic patterns in experimental cerebral concussion. *J. Neurosurg.* 31:34-40, 1969.
4. Hersch, C. Electrocardiographic changes in head injuries. *Circulation* 23:853-860, 1961.
5. Jacobson, S. A. and Danufsky, P. Marked electrocardiographic changes produced by experimental head trauma. *J. Neuropathol. Exp. Neurol.* 13:462-466, 1954.
6. Manning, J. W. and Cotten, M. deV. Mechanism of cardiac arrhythmias induced by diencephalic stimulation. *Am. J. Physiol.* 203:1120-1124, 1962.
7. McLaurin, R. L. and Scott, T. ECG changes after experimental head trauma. *J. Trauma* 15:447-450, 1975.
8. Nadas, A. S., Alimurung, M. M. and Linenthal, A. J. Persistent ventricular pacemaker following basal skull fracture. *Am. Heart J.* 42:888-893, 1951.
9. Ommaya, A. Experimental head injury in the monkey. In: *Head Injury*, Caveness, W. F. and Walker, A. E., editors, pp. 260-275. Philadelphia, J. B. Lippincott Co., 1966.
10. Popovic, N. A., Mullane, J. F., Vick, J. A. and Kobrine, A. Effect of phencyclidine hydrochloride on certain cardiorespiratory values of rhesus monkey (Macaca mulatta). *Am. J. Vet. Res.* 33:1649-1657, 1972.

11. Shatsky, S. A., Alter, W. A. III, Evans, D. E., Armbrustmacher, V. and Clark, G. Traumatic distortions of the primate head and chest: correlation of biomechanical, radiological and pathological data. Society of Automotive Engineers Paper No. 741186. In: Proceedings of the 18th Stapp Car Crash Conference, pp. 351-381. Ann Arbor, Michigan, 1974.
12. Shatsky, S. A., Evans, D. E., Miller, F. and Martins, A. N. High-speed angiography of experimental head injury. J. Neurosurg. 41:523-530, 1974.
13. VanderArk, G. D. Cardiovascular changes with acute subdural hematoma. Surg. Neurol. 3:305-308, 1975.