

Alteration of Postirradiation Hypotension and Incapacitation in the Monkey by Administration of Vasopressor Drugs (35524)

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A transient performance decrement (partial or complete inability to perform a learned task) occurs in monkeys shortly after they are exposed to supralethal doses of ionizing radiation.²⁻⁵ This postirradiation response is commonly referred to as early transient incapacitation (ETI). The temporal sequence of ETI events appears dose dependent.⁴ Generally, ETI in monkeys exposed to radiation doses in the 3- to 30-krad range commences as early as 2 min after exposure and ends 5 to 10 min later with a return to a preirradiation or near preirradiation condition. A significant decrease in blood pressure was also observed immediately following exposure. This hypotension appeared to parallel the development of ETI and a causal relationship was suggested (1). The possibility of eliminating or modifying ETI by maintaining blood pressure with vasopressor drugs was investigated in this study.

Materials and Methods. Male and female monkeys (*Macaca mulatta*), weighing 3-4.5 kg, were used. The conditioning and maintenance of these animals have been previously described.⁶

One week before the animals were irradiated, catheters⁷ were surgically inserted into the abdominal aorta and femoral vein of each monkey. These catheters were used in measuring blood pressure and administering drugs, respectively. The arterial pressure at each observation time was expressed as the mean pressure (half the sum of the values for the systolic and diastolic pressures). Following surgery the monkeys were placed in primate restraining chairs⁸ where they remained throughout the experiment.

Generally, one drug-treated and one control monkey were simultaneously irradiated; however, five of the monkeys were individually irradiated. All monkeys were given unilateral, whole-body irradiations. They were dorsal-ventrally exposed to mixed gamma-neutron radiations delivered as a single pulse of approximately 50-msec duration. The resulting midline tissue dose was 4 krads. The radiation environment⁹ and dosimetry methods¹⁰ have been previously reported.

Animals were judged incapacitated when they lost consciousness. Loss of consciousness was characterized by closing of the eyelids and a forward drooping of the head.

Seven monkeys received only the 4-krad

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² Chapman, P. H., Brooks Air Force Base, Texas, School of Aerospace Medicine, SAM-TR-68-111 (1968).

³ Kaplan, S. J., Gresko, E. M., Bethesda, Maryland, Armed Forces Radiobiol. Res. Inst. Sci. Rep. SR69-9 (1969).

⁴ Seigneur, L. J., and Brennan, J. T., Bethesda, Maryland, Armed Forces Radiobiol. Res. Inst. Sci. Rep. SR66-2 (1966).

⁵ Young, R. J., Chapman, P. H., Barnes, D. J., Brown, G. C., Hurst, C. M., Brooks Air Force Base, Texas, School of Aerospace Medicine, SAM-TR-68-73 (1968).

⁶ Wise, D., and Turbyfill, C. L., Bethesda, Maryland, Armed Forces Radiobiol. Res. Inst. Sci. Rep. SR68-17 (1968).

⁷ Vinyl tubing No. 6179 (i.d., 0.044 in.; o.d., 0.065 in.), Becton, Dickinson and Company, Rutherford, New Jersey.

⁸ Model No. 1206, Foringer and Company, Inc., Rockville, Maryland.

⁹ Sayeg, J. S., (compiler), Santa Barbara, California, Edgerton, Germeshausen and Grier, Inc. Rep. S-260-R (1964).

¹⁰ Dowling, J. H., Bethesda, Maryland, Armed Forces Radiobiol. Res. Inst. Sci. Rep. SR66-3 (1966).

dose of radiation and served as controls for evaluating the effectiveness of vasopressor drug administration. There was no significant difference between the blood pressure and ETI response of irradiated control monkeys infused with saline (volume equivalent to that received by the drug-infused animals) and irradiated noninfused monkeys.¹¹ The vasopressor drug norepinephrine (2 mg/ml) or angiotensin (0.5 mg/ml) was administered to five monkeys using a constant rate infusion pump. Infusion rates for these drugs were 0.115 and 0.42 ml/min, respectively, except where stated otherwise. Infusion commenced approximately 5 min prior to exposure, so that the monkeys were hypertensive when irradiated; mean blood pressure was at least 30% higher than the pretreatment value of approximately 95 mm Hg. After irradiation the flow rate of the infusate was increased in two of the norepinephrine-treated monkeys in an effort to maintain their predrug, preirradiation blood pressure. Drug infusion was stopped in all animals 15 min after irradiation and the blood pressure allowed to fall until the animal became unconscious. Infusion of the drug was then reinstated until consciousness returned. This sequence was repeated several times until the blood pressure no longer responded to drug infusion. Infusion was stopped at this time.

Ephedrine sulfate (2 mg/ml/kg) or amphetamine hydrochloride (1.5 mg/ml/kg) was administered as a single intravenous injection to an additional five monkeys approximately 1 hr before the animals were irradiated. Blood pressure was monitored until death, but no additional attempt was made to maintain the blood pressure near preirradiation values in these monkeys.

Results. Approximately 30 sec after irradiation the mean blood pressure of six of the seven control monkeys began to decrease rapidly, reaching 50 mm Hg or less in about 2.5 to 5 min (Fig. 1a). It was during or immediately following this rapid drop in blood pressure that the six monkeys became comatose and were incapacitated. These monkeys re-

mained unconscious for 10 to 15 min, after which their condition temporarily improved or death promptly ensued. The mean blood pressure of the monkey which did not become incapacitated followed the same pattern seen with the other six except that its mean blood pressure did not fall below 50 mm Hg.

In four monkeys infused with norepinephrine and one infused with angiotensin, the characteristic fall in mean blood pressure after irradiation was not prevented despite preirradiation elevation to as high as 160 mm Hg. However, the severity of postirradiation hypotension was reduced. Figure 1b-f illustrates the first 15-min postirradiation blood pressure response of individual drug-infused animals and their paired controls. None of the four animals infused with norepinephrine displayed any loss of consciousness during the first 15 min postirradiation when the drug was being continuously administered. After 15 min, the infusion of norepinephrine was stopped in all animals and the blood pressure was allowed to fall until the animal became unconscious. Infusion of the drug was then reinstated and consciousness returned. After this sequence was repeated several times, the blood pressure no longer responded to drug infusion and a progressive irreversible hypotension resulted, which terminated in death. In the angiotensin-infused monkey, drug infusion was stopped at 5 min postirradiation (Fig. 1f). By 7.5 min postirradiation, the mean blood pressure had fallen below 50 mm Hg and the animal was unconscious. At this time, infusion of angiotensin was reinstated, the blood pressure rose, and the animal regained consciousness 10 min after irradiation.

The two monkeys treated with ephedrine did not show signs of incapacitation following irradiation. Although the mean blood pressure at the time of exposure was only slightly higher than control values, the hypotension after irradiation was not as severe (Fig. 1g).

Two of the three monkeys treated with amphetamine became unconscious (incapacitated) after irradiation (Fig. 1h). The mean blood pressure of the third remained above 50 mm Hg and it did not show signs of incapacitation.

¹¹ Unpublished data of T. F. Doyle and J. E. Turns, Bethesda, Maryland, Armed Forces Radiobiology Research Institute.

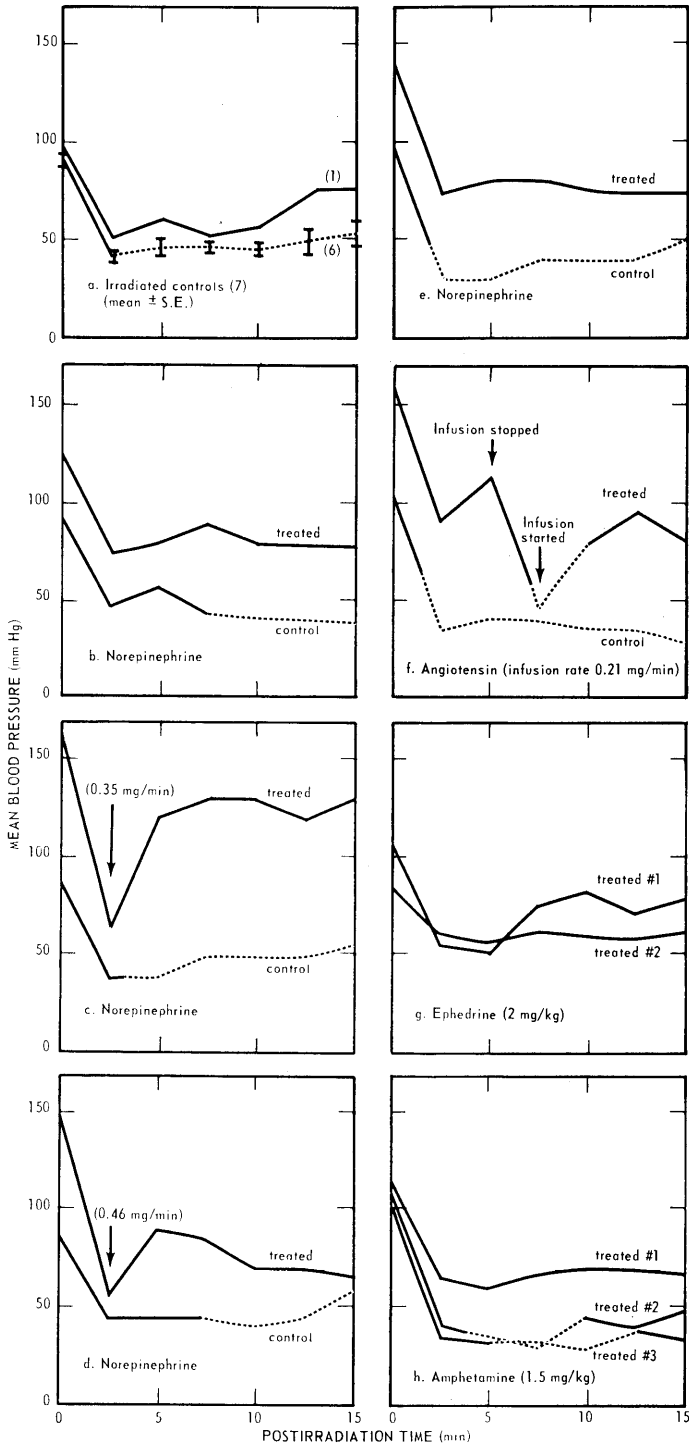


FIG. 1. Mean blood pressure of monkeys after a 4-krad pulsed dose of mixed gamma-neutron radiation. Norepinephrine infusion rate was 0.23 mg/min except where shown (c and d); (---) indicate incapacitation.

Clinically, the ephedrine- and amphetamine-treated monkeys appeared more alert and active before and after irradiation than control monkeys. When the amphetamine-treated animal became incapacitated, the period of incapacitation was brief and the animals appeared more alert and active after recovery than did the control monkeys.

Discussion. The hypotension immediately following supralethal pulsed doses of radiation resembles neurogenic shock seen after severe brain damage resulting from physical trauma (2). Neurogenic shock is characterized by a loss of vasomotor tone, pooling of blood in the extremities, a rapid fall in blood pressure, ischemia to the brain, and a loss of consciousness by the subject. Several of these clinical symptoms were observed in the monkeys of this study. Furthermore, several drugs used in the treatment of neurogenic shock were effective for some time in the irradiated monkeys.

Cerebral blood flow was not measured in the current study. This hemodynamic parameter, however, appears to play a major role in the development of the ETI shock state. Lassen (3) found that the cerebral blood flow in man is independent of changes in the arterial blood pressure within a wide pressure range and that a moderate reduction of blood pressure does not influence cerebral blood flow. Only in marked hypotension with pressures of half the normal value or less is cerebral vasodilation inadequate. When cerebral blood flow falls to a critically low value of about 60% of the control level, clinical signs of cerebral hypoxia then become apparent. Similar findings were reported by Chapman and Young (1) in irradiated monkeys. Immediately (5 min) following a 2500-R dose of cobalt-60 gamma radiation, a precipitous decline (~30% of preirradiation value) in cerebral blood flow occurred, accompanied by parallel changes (~40% of preirradiation value) in systemic blood pressure. Our results are in good agreement with the facts stated above (1, 3). In general, as long as the mean blood pressure was maintained above ~50 mm Hg, the monkeys were alert and active; when the blood pressure fell below this level, the animals lapsed into

unconsciousness. Thus, the critical mean arterial pressure, which must be exceeded if ETI in the monkey is to be avoided, appears to be approximately half the preirradiation, preirradiation pressure.

The dependence of the conscious state on the level of mean arterial pressure was further demonstrated by interrupting and reconstituting drug infusion. This sequence could be repeated a variable number of times. Eventually, however, all animals failed to respond to treatment and abruptly died. The reason for this terminal response is not known; we can only postulate that refractoriness of the cardiovascular system to the drug and/or drug toxicity are involved.

Summary. The effect of vasopressor drugs on the early hypotension and incapacitation observed in monkeys following a 4-krad pulsed dose of mixed gamma-neutron radiation was investigated. Seven monkeys received only the 4-krad dose of radiation and served as controls. Norepinephrine or angiotensin was administered to five other monkeys by intravenous infusion from 5 min prior to irradiation until death, except that infusion was temporarily interrupted several times after irradiation of the animals. Blood pressure was continuously monitored in all animals. Drug-induced blood pressure elevation prior to irradiation did not prevent the characteristic early postirradiation fall in mean blood pressure, but severity of the resulting hypotension was reduced. Cessation of drug infusion after irradiation resulted in a rapid drop in blood pressure with the animal becoming incapacitated (loss of consciousness) when mean blood pressure fell below a critical level of about 50 mm Hg. After drug infusion was resumed, consciousness returned as the blood pressure rose above the critical level. This sequence was repeated several times before the animal failed to respond to drug administration and died abruptly in a hypotensive state. Five other monkeys were given a single intravenous injection of ephedrine or amphetamine 1 hr before irradiation; these animals received no further treatment. Ephedrine administration appeared to be as effective at maintaining satisfactory postirradiation blood pressure and

abolishing ETI as norepinephrine and angiotensin.

The authors express their appreciation to S. L. Bradley, T. F. Doyle, and R. H. Crutcher for their technical assistance during the course of this study.

1. Chapman, P. H., and Young, R. J., *Radiat. Res.* **35**, 78 (1968).
2. Guyton, A. C., "Medical Physiology," p. 489. Saunders, Philadelphia (1964).
3. Lassen, N. A., *Physiol. Rev.* **39**, 183 (1959).

Received Oct. 28, 1970. P.S.E.B.M., 1971, Vol. 137.