

Effectiveness of Pressor Drugs in Beagles Exposed to Mixed Gamma-Neutron Radiations (35358)

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Radiation induced death has commonly been attributed to one of three modes depending on the dose received. These modes are hematopoietic failure, gastrointestinal mucosal loss, or central nervous system changes (1). On the basis of clinical and pathological findings in two individuals dying from radiation doses in excess of 4000 rads (2, 3), Fanger and Lushbaugh (4) have defined a vascular radiation subsyndrome resulting from radiation doses between 5000 and 10,000 rads. This subsyndrome is characterized by hypotension, vascular damage, shock, and death within 2 days.

The hypotension and shock found in the vascular subsyndrome of the two human nuclear accident cases were resistant to treatment by several pressor drugs. Whether this lack of response to pressor agents is a characteristic of the subsyndrome or was a terminal event in these two patients is undetermined. The current study, undertaken to answer this question, characterized the response of irradiated beagles to three pressor drugs. The results of this investigation are reported below.

Material and Methods. Twenty-seven pure bred male beagles, 2 to 3 years old and weighing 10 to 16 kg, were used in this study. The dogs were individually caged in environment-controlled rooms and were conditioned for a minimum of 2 weeks before being placed on the experiment. All animals had free access to water throughout the study and were fed once a day.

The dogs were bilaterally exposed one or two at a time to mixed gamma-neutron radia-

tions from the AFRRI-TRIGA reactor. Uniformity of the radiation field in air at the position occupied by the midline of the animals varied less than 4% from the mean. Depth dose measurements made in tissue equivalent phantoms indicated that the irradiations were Class A (5). Dose rates were selected so that all exposure times were 10 min. Midline tissue doses of 5000 and 10,000 rads were used.

Approximately 60% of the tissue kerma, free-in-air, was attributed to gamma rays, and 40% to neutrons. Depth dose studies indicated that the deposition of energy by the gamma component was similar to that seen with ⁶⁰Co gamma rays. About 75% of the neutron dose was attributed to fast neutrons (greater than 10 keV). The dosimetric techniques and reactor characteristics utilized in this investigation have been previously described.^{2,3}

Since blood pressure and cardiac output measurements were made with the beagles confined to exposure boxes, all dogs were trained to lie quietly for a minimum of 30 min while in the exposure box. Training was usually accomplished in three or four 1-hr sessions.

Four or 5 days prior to irradiation, the beagles were anesthetized with thiopental, and vascular catheters were inserted. The right femoral artery was surgically exposed,

² J. H. Dowling, Experimental determination of dose for the monkey in a reactor pulse environment. SR 66-3, Armed Forces Radiobiology Research Institute, Bethesda, Maryland (1966).

³ J. Sayeg, compiler. Report on neutron and gamma dosimetry measurements at the AFRRI-DASA TRIGA reactor. Report S-260-R, Edgerton, Germeshausen and Grier, Inc., Santa Barbara, California (1964).

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and an 18-in. silicone coated catheter⁴ was advanced through an incision in the artery to the level of the aortic bifurcation. The femoral artery was ligated distal to the catheter. A polyethylene catheter⁵ was inserted into the right jugular vein percutaneously through a 14-gauge needle and advanced to the level of the right atrium. Both catheters were filled with heparin solution (100 units/ml), and the free end of the catheter was knotted until used for blood pressure measurements.

One to 3 days prior to irradiation, base line cardiovascular measurements were obtained. Right atrial pressure⁶ and aortic pressure⁷ were recorded on a physiograph.⁸ A cardiometer⁸ monitored heart rate using the amplifier output from the aortic pressure transducer.

Cardiac output was measured using a densitometer.⁹ Indocyanine green was injected through the right atrial catheter while blood was continuously withdrawn from the aortic catheter using an infusion-withdrawal pump.¹⁰ The optical density of the withdrawn blood was continuously scanned by the densitometer and the results were recorded on a strip chart. When the optical density measurement was completed (approximately 20 ml of blood being scanned) the blood was returned to the aorta.

After aortic pressure, right atrial pressure, and heart rate were recorded, and the cardiac output was calculated, one of three pressor drugs (levarterenol, metaraminol, or phenylephrine) was intravenously administered

through the right atrial catheter, and the measurements were repeated to determine the change, or response, of these parameters to the drug. (These preirradiation measurements on each beagle served as the control or base line values; a minimum of six dogs received each drug.) One-half of the beagles receiving each drug were then exposed to 5000 rads and the other half to 10,000 rads of mixed gamma-neutron radiations. Measurements of aortic pressure, right atrial pressure, heart rate, cardiac output, and of the response to the drug were made 1 or 2 hr after irradiation, and were repeated daily until death of the beagles. (Measurements were not made in the 5000 rad group on the first day following irradiation.)

The following formulas were used in calculating the indicated cardiovascular parameters:

$$\text{Mean pressure} = \text{diastolic pressure} + \frac{1}{3} \text{ pulse pressure,}$$

$$\text{Total peripheral resistance} = (\text{mean arterial pressure} \times 1332) / \text{cardiac output,}$$

$$\text{Stroke volume} = \text{cardiac output} / \text{heart rate.}$$

Means and standard errors were calculated for the physiological values obtained. The significance of the difference between a preirradiation control value and the postirradiation value, as well as the pre- and postirradiation response to metaraminol and phenylephrine, was determined using a *t* test.

Since the action of levarterenol was short, allowing multiple doses to be administered, the responses to this drug were tested by methods of Finney (6). A dose-response regression line was calculated for the preirradiation response and for each postirradiation time this drug was administered. These regression lines were tested and judged parallel; therefore, they were compared by calculating relative potency values which gave the ratio of all equally effective doses. Differences were judged to be significant at the $p = 0.05$ level.

Results. Results of the cardiovascular measurements of the beagles before and after 5000- or 10,000-rad doses of mixed gamma-neutron radiations are summarized in Table I. Systolic, diastolic, and mean pressures were

⁴ Vinyl tubing No. 6209 (id 0.067 in. and od 0.107 in.), Becton, Dickinson and Company, Rutherford, New Jersey.

⁵ Polyethylene tubing PE-160/12 (id 0.045 in. and od 0.062 in.) Clay-Adams, Inc., New York, New York.

⁶ Transducer, model P23BB, Statham Instruments, Inc., Los Angeles, California.

⁷ Transducer, model P23Db, Statham Instruments, Inc., Los Angeles, California.

⁸ Physiograph and cardiometer, 350 series, Sanborn Division, Hewlett-Packard Co., Waltham, Massachusetts.

⁹ Cardio-densitometer, model 350127, Beckman Instruments, Inc., Palo Alto, California.

¹⁰ Model 902, Harvard Apparatus Company, Inc., Dover, Massachusetts.

TABLE I. Values of Physiological Measurements of the Cardiovascular System of Irradiated Beagles.^a

Midline tissue dose (rads)	Postirradiation day tested	Blood pressure (mm Hg)			Heart rate (min ⁻¹)	CO ^b	PR ^c	Stroke vol (ml)
		Systolic	Diastolic	Mean				
Preirradiation		213 ± 7.7	103 ± 3.3	136 ± 4.0	122 ± 6.5	3.2 ± 0.3	3.9 ± 0.2	27 ± 1.9
5000	0	165 ± 8.6 ^f	85 ± 4.6 ^e	110 ± 5.4 ^f	116 ± 8.7	2.0 ± 0.2 ^e	4.9 ± 0.5	18 ± 1.6 ^f
5000	2	173 ± 9.5 ^e	89 ± 5.2 ^d	115 ± 6.2 ^e	100 ± 4.8	2.2 ± 0.2 ^d	4.6 ± 0.5	22 ± 1.5
5000	3	126 ± 12.0 ^f	60 ± 6.4 ^f	88 ± 5.7 ^f	146 ± 9.2	1.4 ± 0.2 ^f	5.9 ± 1.1	10 ± 1.9 ^f
10,000	0	178 ± 8.8 ^f	87 ± 3.7 ^d	116 ± 3.3 ^e	137 ± 13.0	2.4 ± 0.2 ^e	4.2 ± 0.4	20 ± 2.4 ^e
10,000	1	126 ± 14.0 ^f	58 ± 5.2 ^e	86 ± 9.7 ^e	184 ± 18.0 ^d	1.9 ± 0.5 ^d	5.2 ± 1.5	11 ± 2.9 ^e
10,000	2	118 ± 33.0	52 ± 9.3 ^e	78 ± 16.0 ^d	179 ± 20.0	1.8 ± 0.5 ^d	3.9 ± 0.7	11 ± 4.7 ^e

^a Mean ± standard error.^b Cardiac output (liters/min).^c Peripheral resistance [(dyne-sec)/cm²] × 10⁻³.^d *p* < .05.^e *p* < .01.^f *p* < .001.

lower 1 to 2 hr postirradiation than before irradiation. These values had further decreased when the last measurement was taken approximately 12 and 18 hr before death of the beagles receiving 5000 and 10,000 rads respectively. Increased heart rate was noted in all measurements made in the beagles exposed to 10,000 rads (only significant on day 1) and on day 3 of the 5000 rad group. Right atrial pressure generally decreased after irradiation. Irradiation caused a decrease in cardiac output and stroke volume. Total peripheral resistance remained relatively constant in the dogs receiving 10,000 rads but increased slightly although not significantly in the dogs receiving 5000 rads.

The regression line obtained by plotting log dose of phenylephrine against the maximum increase in systolic pressure above the predrug pressure in unirradiated beagles was similar to the ones obtained at all postirradiation testing times following both 5000 and 10,000 rads.

The effectiveness of metaraminol in increasing systolic pressure was similar in unirradiated and irradiated beagles. A dose of 0.1 mg/kg of metaraminol increased systolic pressure 100 to 140 mm Hg above the predrug systolic pressure, while a dose of 0.2 mg/kg increased systolic pressure 150 to 180 mm Hg. Although the response to both phenylephrine and metaraminol was similar before and after the beagles were irradiated, the systolic pressure resulting from a given dose of drug was less after irradiation than before since the systolic pressure in the irradiated dogs was lower when the drug was administered.

The regression lines obtained by plotting the log dose of levarterenol against the maximum increase in systolic pressure above the predrug pressure are illustrated in Fig. 1. The lines obtained from the measurements on day 0 following 5000 and 10,000 rads were similar, as were those obtained on days 2 and 3 after 5000 rads and days 1 and 2 after 10,000 rads. The relative potencies for these two regression lines (compared to the preirradiation one) were 0.7 and 0.4, respectively, indicating that the effectiveness of levarterenol increased in irradiated beagles compared to the preirradiation controls (*p* < 0.05).

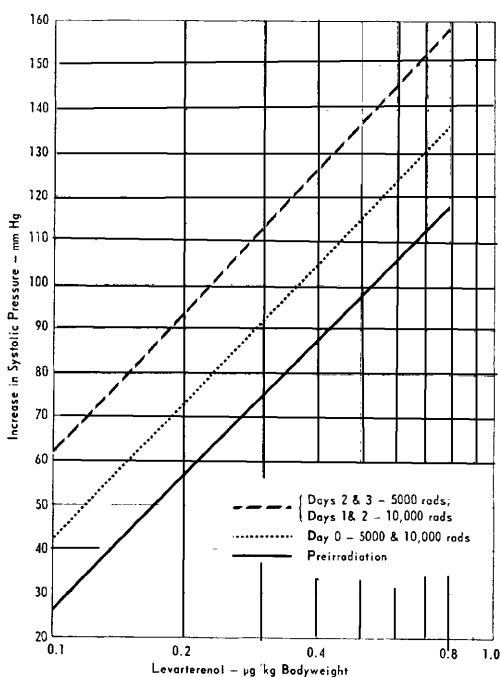


FIG. 1. Maximum increase of systolic pressure of unirradiated and irradiated beagles to levarterenol.

Mean values of heart rate, systolic pressure, stroke volume, and peripheral resistance in unirradiated and irradiated beagles are illustrated in Fig. 2 along with the effect of 0.2 $\mu\text{g}/\text{kg}$ of levarterenol, 0.1 mg/kg of metaraminol, and 0.1 mg/kg of phenylephrine on these cardiovascular parameters. Too few dogs survived until day 2 following 10,000 rads to permit statistical analysis of drug response; therefore none of these data were plotted. All three drugs generally reduced the heart rate of irradiated beagles to less than the preirradiation, predrug base line, and restored systolic pressure to at least the base line value. All three drugs except phenylephrine in the dogs receiving 10,000 rads increased stroke volume of irradiated dogs. In general, until a terminal state was reached all three drugs increased peripheral resistance of the beagles receiving 5000 rads to the same extent or greater than that of unirradiated beagles, while the change of peripheral resistance from drug administration in the dogs receiving 10,000 rads was approximately equal to the response of unirradiated controls.

Discussion. Alterations occur in physiological parameters of the cardiovascular system of irradiated animals when compared to unirradiated controls. Caster *et al.* (7) observed an altered electrocardiogram and an increased plasma volume of rats receiving 700 R. Andrews and Brace (8) reported a change in the heart rate and electrocardiogram of guinea pigs receiving 25,000 R. Phillips and Kimeldorf (9) observed that smaller doses of radiation were required to produce changes in the peripheral blood pressure of rats than to produce a change in aortic pressure, and they suggested that the first response of the cardiovascular system to radiation occurs in the peripheral circulation. Kundel (10) reported that doses of 1950 to 6600 rads in monkeys caused a decrease in blood pressure. Since the response of these irradiated monkeys to norepinephrine was less than in unirradiated controls, Kundel suggested a direct effect of radiation on the peripheral vessels.

Some authors have proposed that histamine release causes the fall in blood pressure in irradiated animals (11), while others have suggested a depression of the central nervous system (12), especially the autonomic centers (13, 14), by radiation.

In studies on dogs in which only the heart area was irradiated (15-18), changes in the electrocardiogram, atrial pressures, and blood pressure occurred 1 to 2 weeks postirradiation. These changes were usually attributed to necrosis of the ventricles. Larger doses of radiation were needed to cause measurable changes when only the heart was irradiated than in studies using whole body irradiation. Since increased right atrial pressure is the earliest sign of heart failure, the normal and decreased right atrial pressure in the current study, indicates adequate functioning of the heart as a pump. It is, therefore, unlikely that the changes reported here are due to a direct effect of radiation on the heart.

Although the measured and calculated parameters of the cardiovascular system of beagles in the current study changed after irradiation, the pressor agents used were generally effective in restoring these parameters to at least the preirradiation, predrug base line levels. All three drugs are known to

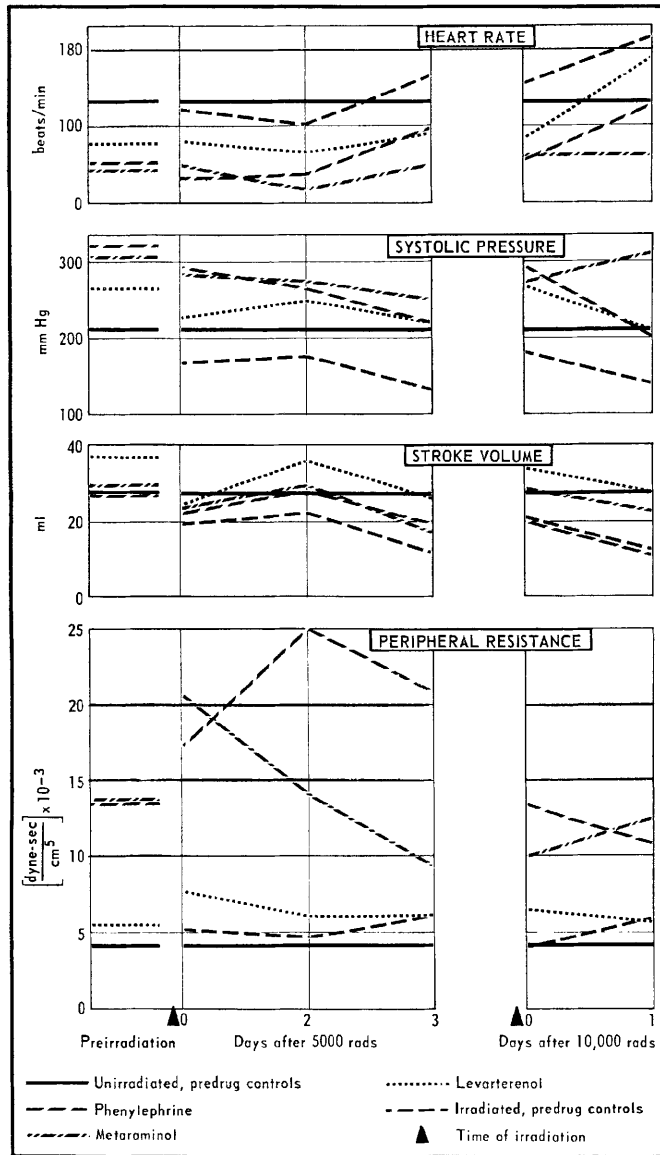


FIG. 2. Effect of pressor drugs on heart rate, systolic pressure, stroke volume, and peripheral resistance of irradiated beagles. Unirradiated, predrug baseline values are extended to aid in comparing these values with postirradiation ones.

increase blood pressure by constricting peripheral arterioles and increasing peripheral resistance. While levarterenol was the most effective of the three drugs in increasing blood pressure, this drug increased peripheral resistance less than the other two. The

mechanism of more effective action of levarterenol is not evident from these results.

Since peripheral resistance did, not decrease in irradiated animals, the findings of this study conflict with the theory that radiation-induced hypotension is caused by dilata-

tion of peripheral blood vessels. Furthermore, the peripheral vessels are capable of constricting as evidenced by the response to pressor drugs. These doses of radiation may affect the normal autonomic response to hypotension so that peripheral resistance is not increased sufficiently to overcome the radiation-induced hypotension, or changes in blood viscosity might cause an apparent normal peripheral resistance even though dilatation of peripheral vessels occurred. However, the pressor drugs used were effective agents in the normal therapeutic dose range in elevating blood pressure, and lack of response to these drugs in irradiated animals is probably a terminal event that occurs shortly before death.

Several factors known to contribute to blood pressure regulation were not studied. These include blood volume, blood viscosity, and the elasticity of the arteries. Since changes in the elasticity of the arteries would mainly affect diastolic pressure, a radiation-induced change in this factor is not likely to explain the changes in systolic and diastolic pressures found in irradiated animals. Although fluid losses from vomiting and diarrhea probably result in hemoconcentration in irradiated animals, the significance of this factor in influencing blood pressure is not clear. Montgomery and Warren (12) reported that the hematocrit and blood volume changes occurring in irradiated rats 6 and 30 hr after 1500 to 2500 R of X-rays were not sufficient to explain the blood pressure changes, while Caster *et al.* (7) reported increased plasma volume in irradiated rats 6 to 10 days after 700 R of X-rays. Therefore, further investigation of blood volumes and viscosities in irradiated animals would contribute to a better understanding of the mechanism of radiation induced hypotension.

Summary. Aortic pressure, right atrial pressure, heart rate, and cardiac output were measured; and mean pressure, stroke volume, and peripheral resistance were calculated in 27 male beagles before and after 5000- or 10,000-rad whole body doses of mixed gamma-neutron radiations. The response of these beagles to levarterenol, phenylephrine, or metaraminol was also determined before and

after irradiation. Irradiation caused a decrease in aortic pressure, cardiac output, and stroke volume; and an increase in heart rate. Peripheral resistance increased, but not significantly, in irradiated beagles. Phenylephrine and metaraminol were equally effective before and after the dogs were irradiated, while levarterenol was more effective in irradiated dogs. The results are interpreted as follows: (i) radiation induced hypotension cannot be fully explained by radiation effects on peripheral blood vessels; (ii) pressor drugs are effective in irradiated beagles with hypotension, and drug effectiveness is probably decreased only as a terminal event shortly before death; (iii) any direct effect of radiation on the heart is of limited significance in whole body exposure.

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