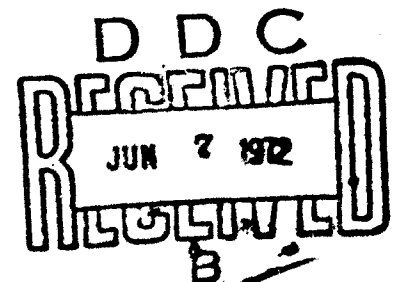


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**AFRRI
SCIENTIFIC
REPORT**

**CANINE CARDIOVASCULAR
HOMEOSTASIS IN THE
GASTROINTESTINAL RADIATION
SYNDROME**

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**ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
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FOREWORD
(Nontechnical summary)

The gastrointestinal radiation syndrome terminates in cardiovascular collapse. The initiating and one of the persisting factors present during the development of this syndrome is, no doubt, the structural breakdown of the small intestine. However, there is a lack of understanding about the mechanisms which modify the dynamic state of the circulatory system and eventually cause its irreversible deterioration. In this study the functional capacity of the dog heart and the cardiovascular regulation after exposure to 1500-rad whole-body pulsed gamma-neutron radiation were investigated. A significantly decreased output of blood volume from the heart and an increased total peripheral resistance of the blood vessels were observed 72 hours postirradiation. The mean blood pressure was still maintained near to the preirradiation level; however, the left ventricular work output meanwhile decreased to about 50 percent of the preirradiated level. The hemodynamic regulation of blood flow to blood pressure relationship showed an altered pattern after epinephrine injection. At 48 hours postirradiation epinephrine induced an extremely prolonged high elevation of blood pressure. After 72 hours the regulatory process further deteriorated; however, still without indication of injury to the heart. This study supports the concept that functional vascular alterations underlie the development of the so-called gastrointestinal radiation syndrome.

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ABSTRACT

Beagles were subjected to 1500 rads of whole-body pulsed gamma-neutron radiation. Forty-eight and seventy-two hours later the animals were anesthetized and the major cardiovascular parameters were obtained. Thereafter, the hemodynamic regulation was studied after intravenous administration of 5.0 $\mu\text{g/kg}$ epinephrine. It was observed that at 48 hours postirradiation, the major cardiovascular parameters were unchanged. After 72 hours, with the exception of the mean blood pressure, significant hemodynamic deterioration developed. The average stroke volume and stroke work decreased 50 percent as compared with the control nonirradiated average values. The median total peripheral resistance, meanwhile, increased in the same magnitude. The blood pressure response after epinephrine was prolonged and significantly higher at 1 minute postinjection in the 48-hour group. The vagal reflex bradycardia became less expressed. After 72 hours postirradiation the epinephrine-induced cardiovascular regulation was further deteriorated. The epinephrine effect demonstrated that in the gastrointestinal radiation syndrome prior to the cardiovascular collapse, a latent imbalance of alpha and beta adrenergic activity is already present. The data indicate further that the cardiovascular deterioration is peripheral rather than myocardial in origin. This study supports the concept that functional vascular alterations underlie the development of the so-called gastrointestinal radiation syndrome.

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I. INTRODUCTION

There is sufficient evidence in the literature to indicate that the gastrointestinal radiation syndrome terminates in cardiovascular collapse.^{4, 16, 24} The initiating and one of the persisting factors present during the 4-day survival period is, no doubt, the structural breakdown of the small intestine.³⁷ However, the progressive intestinal morphological deterioration is not directly correlated with the progress of this clinical picture. According to Iushbaugh,³¹ "Intestinal mucosal loss would seem to have little relation to the underlying lesion which must be located in the vascular system." The role of the cardiovascular system in the radiation sequelae has been underemphasized by many investigators, possibly because circulatory deterioration could be masked by the cardiovascular reserve.^{9, 13} The mechanism of hemodynamic homeostasis during the postirradiation period and the steps which eventually lead to irreversible deterioration of the cardiovascular system, therefore, remain to be explored.

The objective of this study was to obtain information about the involvement of the cardiovascular system in the development of the gastrointestinal radiation syndrome. Since overt cardiovascular disturbances are rarely observed until the terminal stage, a superimposed cardiovascular stress (exogenous epinephrine) has been employed to test the responsiveness and depth of the reserve capacity of irradiated animals. In this manner, it was believed possible to reveal a compensating but deteriorating hemodynamic mechanism.

II. MATERIALS AND METHODS

Eighteen male beagles, 12-14 months old and weighing 9.5-11.5 kg, were used in this study. The dogs were divided into three equal groups: (1) nonirradiated, control

group; (2) irradiated group, submitted to experimental procedures 48 hours postirradiation; and (3) irradiated group, studied at 72 hours postirradiation. Food was withheld from all the dogs overnight before irradiation. Water was available ad libitum. At approximately 1 hour before irradiation the animals were placed in Lucite restraining cages and transferred to the exposure room of the AFRRI-TRIGA reactor where they received 1500 rads midline tissue dose of pulsed mixed gamma-neutron radiation. The dogs were positioned on an isodose exposure curve about the reactor core with the center line of the restraining cages 200 cm from the vertical core center line. The AFRRI-TRIGA reactor and exposure facilities have been described elsewhere.³⁹ The midline tissue dose for each exposure was calculated as the product of the two factors: tissue kerma, free-in-air, times 0.81. The variation in tissue kerma, free-in-air, from position to position in each exposure group was less than 4 percent from the mean. Approximately 60 percent of the tissue kerma, free-in-air, was from gamma radiations having an effective energy between 1 and 2 MeV. Approximately 10 percent was from neutrons with energies greater than 3 MeV, 10 percent from neutrons with energies between 1.5 and 3 MeV, 10 percent from neutrons with energies between 0.01 and 1.5 MeV, and 10 percent from slower neutrons. About 80 percent of the dose was delivered in less than 70 milliseconds. The method for dosimetry was delineated by Pitchford and Thorp.³⁶ After exposure, the dogs were returned to their cages. During the postirradiation period, all animals were free to consume food and water ad libitum. The experimental procedure was performed at the same time of day for all animals.

Anesthesia was induced by intravenous injection of 30 mg/kg sodium pentobarbital (Nembutal). After a midline incision on the neck region the trachea was opened and a tracheal cannula was inserted which was connected to the oxygen consumption analyzer. The right carotid artery and jugular vein (down to the right atrium) were cannulated and the blood was directed through the cuvettes of an arteriovenous oxygen difference analyzer. The blood was pumped back into the systemic circulation via the right femoral vein. Figure 1 shows the experimental setup. An analog computer

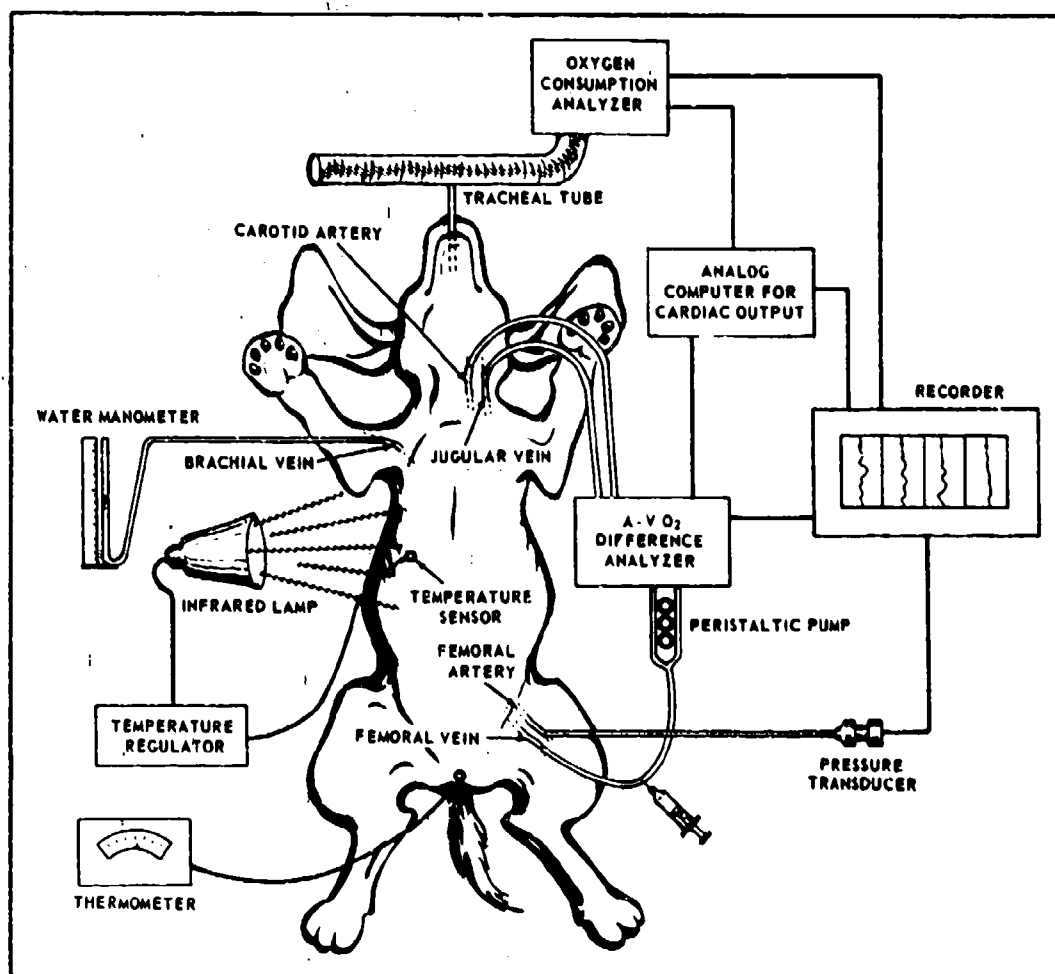


Figure 1. Experimental setup

(which is the third part of the continuous cardiac output analyzer, Oxford Instrument Company, Jackson, Mississippi) calculated the cardiac output from the information continually recorded by the two other instruments utilizing the Fick principle.^{14, 15}

The extracorporeal shunt of polyethylene tubing was filled with a heparinized saline solution and the animals received a total dose of 10,000 units of heparin. Arterial blood pressure was recorded from the femoral artery by a Statham pressure transducer (Model No. P23Db).

The body temperature of the animals was maintained at 37°C with the aid of an infrared lamp connected through an automatic thermoregulator to a temperature sensor. The experimental procedure began after a control period following completion of the surgical procedures.

The following parameters were continuously recorded by an electronic recording system (Brush Instruments Division, Cleveland, Ohio) or calculated as follows:

(1) Systemic arterial blood pressure (millimeters of mercury) analyzed for (a) systolic blood pressure; (b) diastolic blood pressure; (c) mean arterial blood pressure (calculated from the diastolic blood pressure + 1/3 pulse pressure); (d) pulse pressure (the difference between the systolic and diastolic blood pressures).

(2) Heart rate (beats per minute) obtained from the blood pressure record.

(3) Total oxygen consumption (milliliters of oxygen per minute).

(4) Arteriovenous oxygen difference (percent of oxygen in 100 ml of blood).

(5) Cardiac output was calculated in accordance with the Fick equation (milliliters per minute) by dividing the rate of oxygen consumption by the arterio-venous oxygen difference.

(6) Cardiac index (milliliters per minute per square meter) calculated by dividing the cardiac output by the surface area (where surface area = $0.112 \times 2/3$ body weight).¹¹

(7) Left ventricular stroke volume (milliliters per beat) calculated as: cardiac output/heart beats per minute.

(8) Stroke work (left ventricle work) was calculated in gram meters per stroke according to the following equation:

$$\text{stroke volume} \times \frac{\text{mean blood pressure (millimeters of mercury)}}{1000} \times 13.6.$$

(9) Total peripheral resistance was computed in absolute units (dynes sec cm^{-5}) by the formula of $\frac{\text{mean blood pressure} \times 1332}{\text{cardiac output (milliliters per second)}}$

After taking the initial control values, epinephrine (U.S.P. 1:1000) was injected intravenously in a single dose of $5.0 \mu\text{g/kg}$ and the subsequent hemodynamic changes were observed in minute intervals.

Statistical analysis of the data obtained in this study was performed utilizing a Scientific Data Systems 920 digital computer. This computer was programmed to calculate means and standard deviations and to perform a paired t-test analysis.

III. RESULTS

As may be observed in Table I, the hemodynamic parameters studied at 48 hours postirradiation were still in the same range as those of the nonirradiated control

Table I. Hemodynamic Alterations Induced by 1500 Rads Pulsed Gamma-Neutron Whole-Body Irradiation in Beagle Dogs (see text for units)

	Nonirradiated	Irradiated			
	Control values (mean $\pm$ S. D.)	48 hours postirradiation (mean $\pm$ S. D.)	Percent of control	72 hours postirradiation (mean $\pm$ S. D.)	Percent of control
Systolic blood pressure	160.3 $\pm$ 21.3	179.7 $\pm$ 8.2	112.1	160.3 $\pm$ 9.6**	93.8
Diastolic blood pressure	120.5 $\pm$ 17.0	140.3 $\pm$ 10.8†‡	116.5	106.3 $\pm$ 6.4**	88.2
Mean blood pressure	133.8 $\pm$ 18.3	153.4 $\pm$ 9.8†‡	114.6	121.0 $\pm$ 7.2**	90.5
Pulse pressure	39.8 $\pm$ 6.2	39.3 $\pm$ 4.7	98.8	44.0 $\pm$ 4.9	110.5
Heart rate	159.0 $\pm$ 17.7*	161.8 $\pm$ 15.6	101.6	183.3 $\pm$ 7.7**	115.2
Cardiac output	1508.3 $\pm$ 320.0*	1575.0 $\pm$ 293.2	104.4	905.0 $\pm$ 176.5**	60.0
Cardiac index	2.42 $\pm$ 0.19*	2.66 $\pm$ 0.20	110.0	1.66 $\pm$ 0.16**	68.7
Stroke volume	9.5 $\pm$ 1.9*	9.9 $\pm$ 2.3	104.2	4.9 $\pm$ 1.0**	51.6
Stroke work	17.2 $\pm$ 3.6*	20.6 $\pm$ 5.2	119.8	8.1 $\pm$ 1.7**	47.1
Total peripheral resistance	7391 $\pm$ 2026*†	8029 $\pm$ 1667	108.8	11062 $\pm$ 2383**‡	149.7
Oxygen consumption	103.5 $\pm$ 19.7**†	113.5 $\pm$ 15.7	109.7	77.5 $\pm$ 14.9**	74.9

* Significant difference compared to 72 hours postirradiation ($p < 0.01$)

† p value $0.025 > p > 0.01$

‡ Significant difference compared to control ($p < 0.01$)

§ p value $0.05 > p > 0.01$

** Significant difference compared to 48 hours postirradiation ($p < 0.01$)

values. However, after 72 hours definite alterations took place. With the exception of the blood pressure values significant changes occurred in all measured parameters (Table I). The median stroke volume decreased about 50 percent below the control values possibly reflecting a decreased blood volume and a compensatory tachycardia. The median heart rate increased significantly, slightly improving the median cardiac output and preventing its decrease below 60 percent of the control values. Since the median mean blood pressure did not change significantly, the decreased stroke volume reflected a proportionate decrease in the median stroke work. The compensatory increase in peripheral resistance prevented further deterioration in cardiac output. Figure 2 represents the above described percentage changes. When

the values for the 72 hours cardiac output were correlated to the corresponding body weight and surface area the resulting cardiac index decreased only about 30 percent from the preirradiation values. This change corresponded well with the median oxygen consumption alteration.

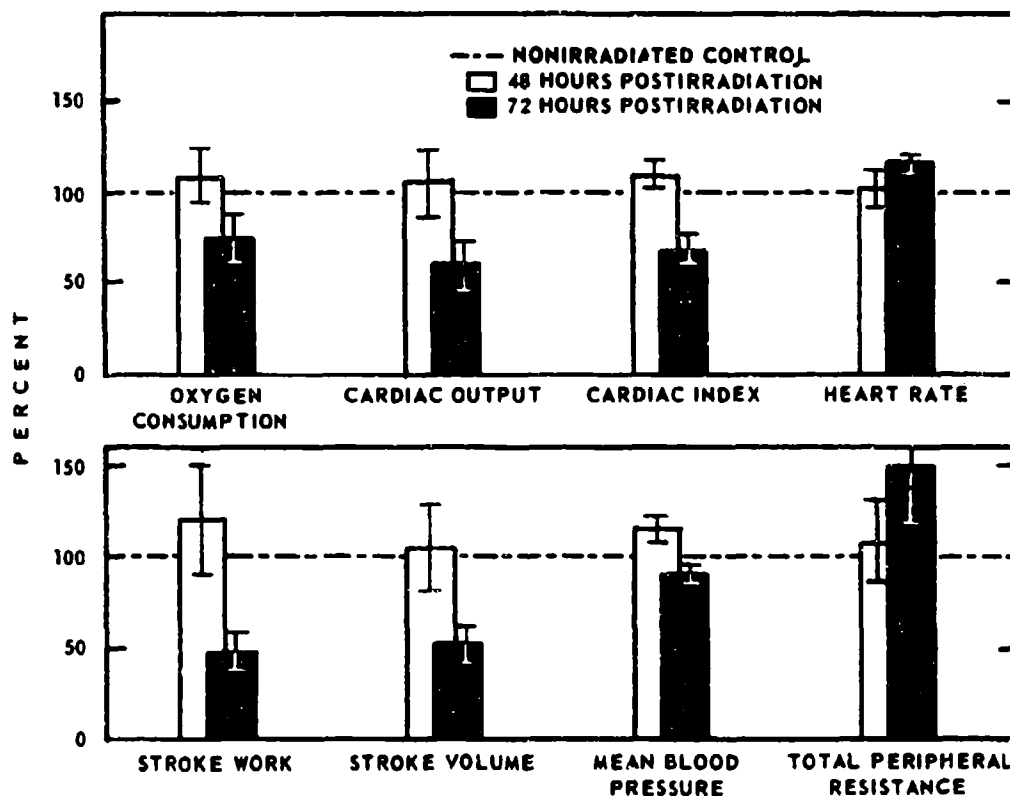


Figure 2. Percent representation of the hemodynamic alterations induced by 1500 rads pulsed gamma-neutron whole-body irradiation in beagle dogs. Absolute values are presented in Table I.

After obtaining the hemodynamic values of the control and irradiated groups, 5.0 $\mu\text{g/kg}$ epinephrine were injected intravenously. The alpha and beta adrenergic responses were well observable in all groups. In Figure 3, we plotted the median mean blood pressure and heart rate values against the corresponding median stroke volume at 1-minute intervals. The hemodynamic regulation appears to be altered

48 hours postirradiation. There was an extremely high blood pressure response after 1 minute which however, similar to that in the controls, returned approximately linearly toward preinjection values (Figure 3) or, in other words, the ascending and the descending slopes were parallel. The magnitude of the stroke volume response after 1 minute is significantly less than the control. The reflex vagal bradycardia is also less reduced at 48 hours postirradiation, although still with a clear indication of the existing exponential relationship with the stroke volume alterations. At 72 hours postirradiation the hemodynamic regulation is completely altered after epinephrine injection. Although the blood pressure response after 1 minute was not significantly

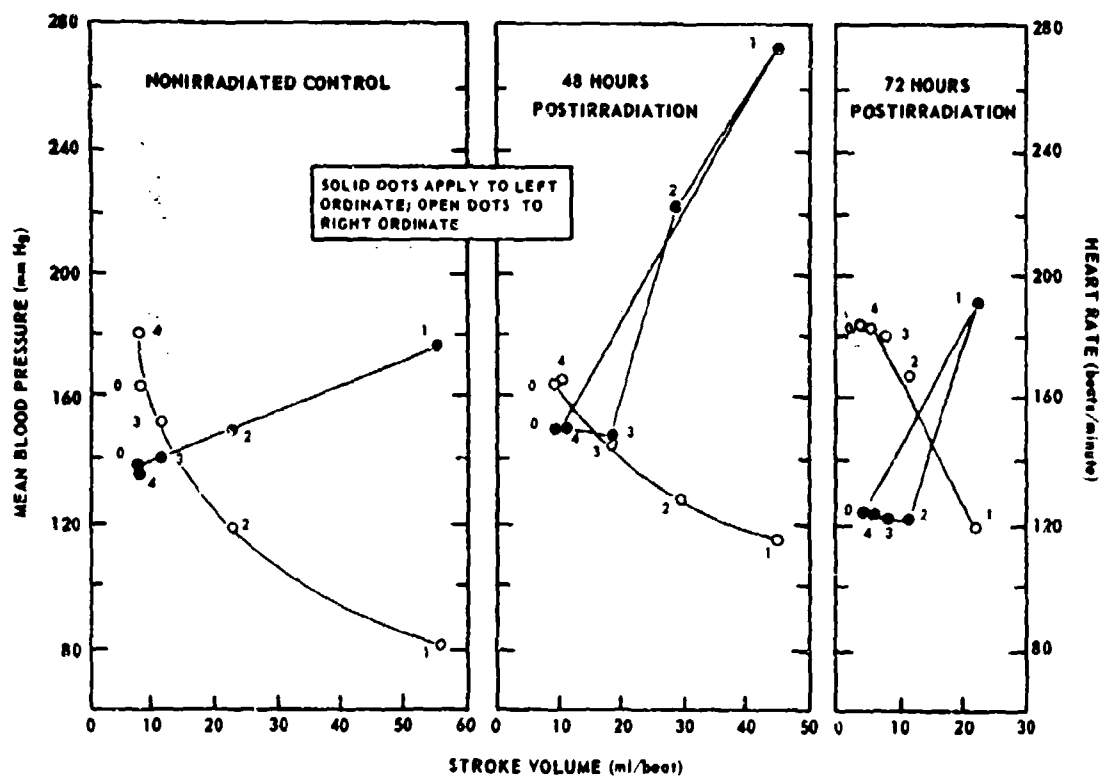


Figure 3. Hemodynamic regulation after 5.0 µg/kg epinephrine. The median values of mean blood pressure and heart rate are plotted against the corresponding values of stroke volume in minute intervals.

altered from the control, its return to preinjection values was shorter and not linear with the stroke volume changes. After a 1-minute peak it returned to the preinjection level despite the still increased stroke volume levels. A decreased reflex bradycardia was also present with a noticeable linear relationship with the stroke volume responses.

When the induced cardiac output changes were plotted against the blood pressure responses it became clear that after 72 hours postirradiation the cardiac output as related to the blood pressure was maintained disproportionately higher compared with the control and 48-hour values (Figure 4). It is interesting that in all groups the

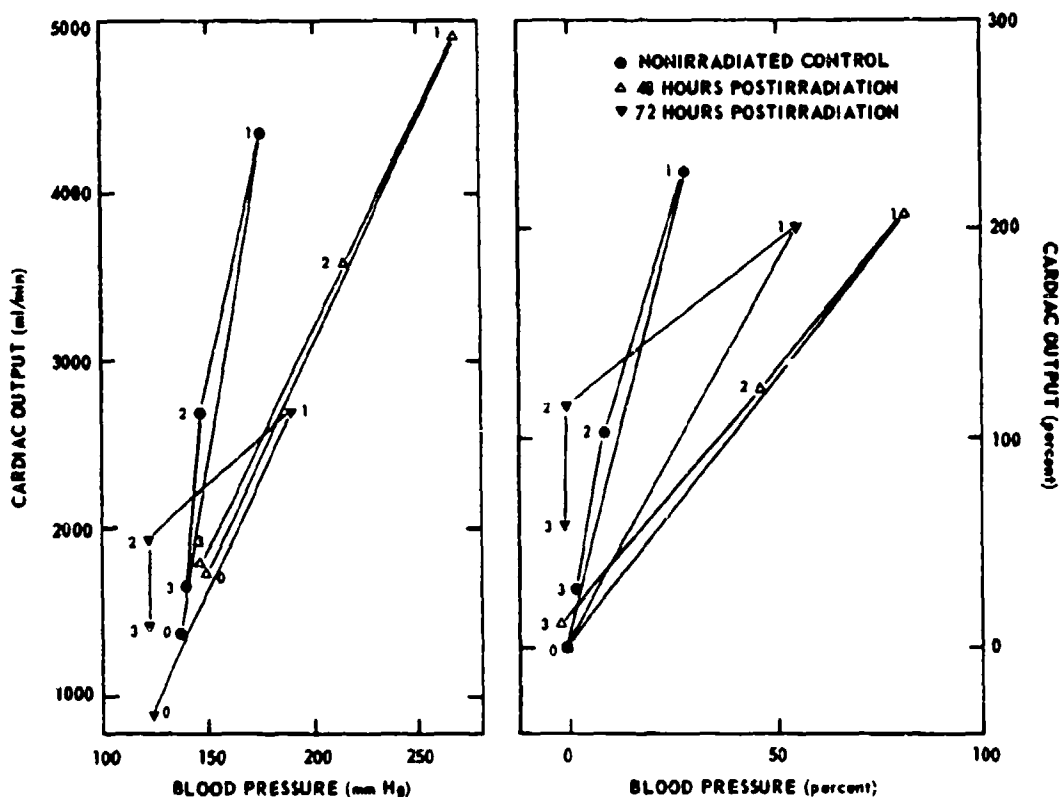


Figure 4. Relationship between median cardiac output and median mean blood pressure alterations induced by 5.0 $\mu\text{g/kg}$ epinephrine I.V. injection. Values are presented in minute intervals.

induced cardiac output changes at the 1-minute peak were the same if they were calculated as percent change of the initial level.

The epinephrine-induced prolonged elevation of cardiac output after 72 hours postirradiation is well reflected in the total peripheral resistance pattern. Figure 5 shows that the resistance of the 72-hour group is still decreased at the 2-minute interval when the vasoconstriction phase has already taken place in the nonirradiated group.

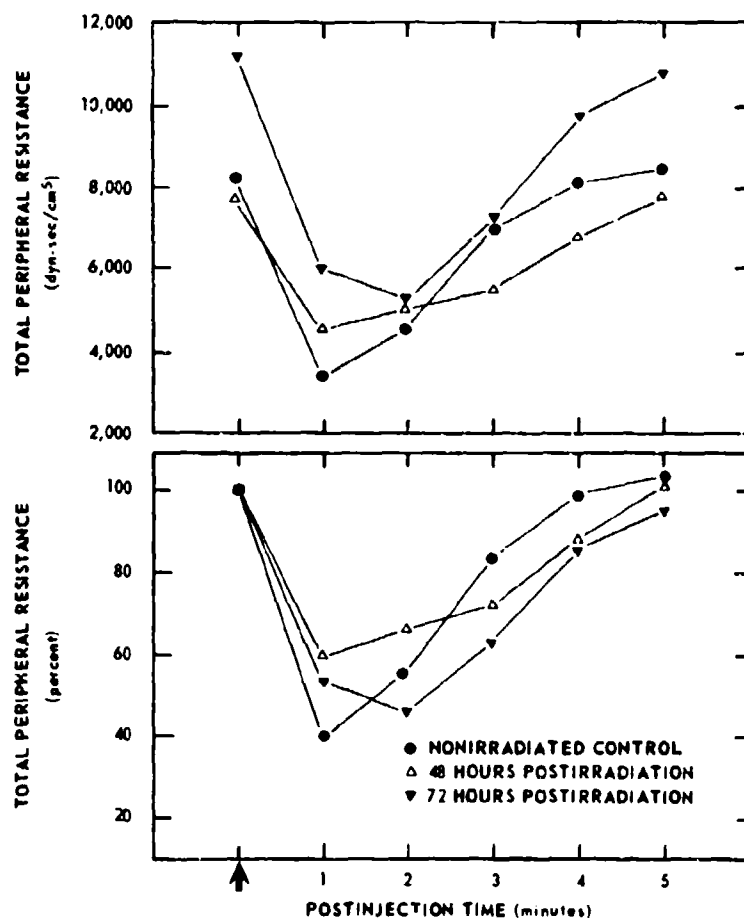


Figure 5. Median total peripheral resistance changes in minute intervals induced by 5.0 μ g/kg epinephrine I. V. injection

In comparison to these changes in peripheral resistance (which reflect significant alteration of the peripheral vasoactivity) the epinephrine-induced stroke work alterations may not indicate yet myocardial alterations (Figure 6). Although in absolute units the stroke work response was significantly lowered at 72 hours postirradiation, when it was expressed in percent of its initial level, the response was proportionate to the nonirradiated group.

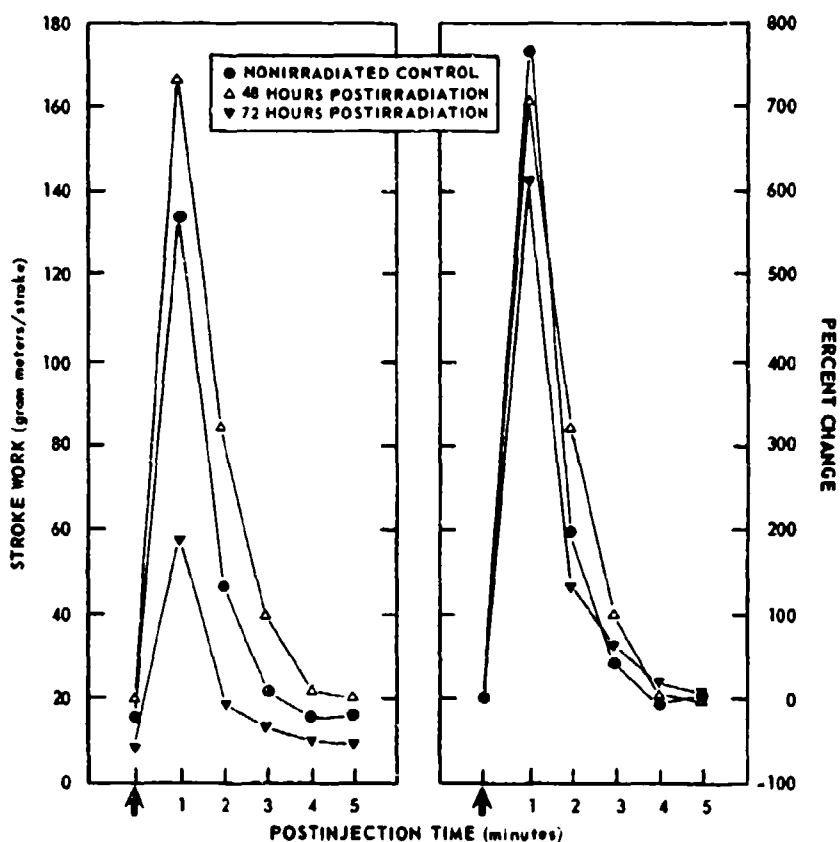


Figure 6. Postinjection alterations of the median stroke work induced by 5.0 $\mu\text{g/kg}$ epinephrine I.V. injection expressed in absolute units and percent of the preinjection level

IV. DISCUSSION

Although radiation-induced circulatory deterioration may exist early, it is not physiologically manifested because of the large cardiovascular reserve capacity.^{9, 13} This could be the reason that the contribution of the circulatory system toward the development of this acute radiation sickness was not recognized in earlier studies. It became clear, however, in view of recent research^{29, 35} that cardiovascular alteration plays a role in the development of the gastrointestinal radiation sickness of the animal. This experimental evidence was strongly supported by clinical data.^{7, 22} Lushbaugh³¹ concluded that the underlying lesion must be located in the vascular system and he introduced the concept of the vascular damage syndrome.

It appears that even when subjected directly to supralethal doses of radiation, the heart is strongly radioresistant.^{2, 41} Dog hearts were exposed locally to 20,000 R of ⁶⁰Co radiation and no evidence was found of functional deterioration of the ventricles during the first 14 days following irradiation.⁴⁰

This may suggest that the results obtained in the present experiment were probably not induced by direct radiation effects but rather by indirect effects of radiation on the heart. These indirect effects could have several areas of origin. Guyton¹² states "that oxygen need by the tissues is perhaps the most important common denominator in the regulation of cardiac output." Indeed, the cardiac output and, even better, the cardiac index corresponded well with the decreasing total body oxygen consumption. The irradiated dogs after the 3rd day showed a loss of body weight of about 5 percent of the preirradiated values. Diarrhea was present but not excessive. Autopsy did not reveal intestinal hemorrhage. A statistically significant but relatively

small hemoconcentration developed. This observation is in agreement with Lukin's work³⁰ which showed an approximate 10 percent loss of plasma in dogs on the 3rd day after 1000 R of irradiation. The significantly large decreased cardiac output was most likely induced by radiation-induced metabolic changes, and the developing hypovolemia may well have been a contributory factor.

As the cardiac output decreased, the heart rate increased significantly in an attempt to compensate for it. In addition, the lowered cardiac output was balanced by an increased peripheral resistance to maintain the mean blood pressure approximately near the preirradiation level. Similar events of change were described by others.^{16,29} However, if this type of compensation is functioning for a prolonged period of time, the extreme vasoconstriction might lead to persistent tissue hypoxia.¹⁹ Indeed, at 72 hours postirradiation when the animals entered into the terminal phase, prolonged increased peripheral resistance may have initiated an ischemia resulting in death within 10-15 hours thereafter.

It is unlikely that the increased total peripheral resistance uniformly reflects a general vasocompensatory process by maintaining the adequate blood pressure level against the decreased cardiac output. Indeed, disproportionately increased splanchnic vasoconstriction was measured in irradiated rats.^{19,20} This phenomenon is commonly observed also in different types of shock with extracardiac origin.^{1,17} The significance of this observation is enhanced by the fact that development of small intestinal ischemia has been connected with the irreversibility of cardiovascular deterioration.^{27,28} Increased viscosity and obstruction of the vessels may also

contribute toward the vascular resistance. Eddy and Casarett⁵ observed formation of plugs in the rat intestinal capillaries after a supralethal dose of radiation.

Epinephrine as an alpha and beta adrenergic agent is a classical compound in experimental physiology and pharmacology. The overall hemodynamic effect depends on its dose and to a certain extent on the intact vagal reflex.³ The altered hemodynamic regulation after epinephrine administration in our experiment does not necessarily indicate myocardial injury. Indeed, the response of the Langendorff isolated heart preparation (rat, guinea pig, rabbit) to various autonomic agents showed no consistent changes even when studies were carried out several days after supralethal x-ray exposures.⁶ The decreased vagal reflex activity in the irradiated animals after epinephrine injection is either the consequence of the irradiation produced inhibition of nerve conductivity³⁴ or may be the result of a peripheral alpha receptor oversensitivity and/or alpha and beta receptor imbalance. Probably, the second possibility is valid and supported by the following facts. There are indications that the irradiated animals' blood vessels develop extreme reactivity to constrictor stimuli.²³ Furthermore, data collected during the postirradiation period showed neurohumoral imbalance.⁴³ A general change in the content of epinephrine and norepinephrine of various tissues was recently reported in irradiated animals.^{32,44} Goodall and Long¹⁰ showed that the physiological demand for epinephrine and norepinephrine is so great after irradiation that the adrenal gland is partially or completely depleted of its catecholamine reserve; however, the biosynthesis of these hormones does not decrease; if anything, it increases. Similar observations were made about the adrenal cortex⁸

concerning production of glucocorticoids. Furthermore, Zwelfach and Kivvy-Rosenberg⁴⁵ indicated that, after whole-body irradiation, responses of terminal arterioles and precapillaries to epinephrine and norepinephrine are exaggerated. We also saw indications of similar etiology in a previous experiment concerning the small intestinal vascular responses of irradiated dogs after administration of norepinephrine.²¹ The present study therefore substantiates the existence of a neurohumoral imbalance. Forty-eight hours postirradiation we observed an extremely large blood pressure response after epinephrine injection. At this time, however, the hemodynamic values were still in the normal range. It is interesting that Ryzewski³⁸ reported no exaggerated blood pressure responses in dogs exposed to 800 R of x rays. Apparently, cardiovascular changes as well as specific gastrointestinal injury are manifested at higher radiation doses.

Although the functional capacity of the heart decreased after 72 hours postirradiation to about 50 percent of the preirradiation level, this is still not necessarily an indication of myocardial failure. Experiments^{9, 13} proved that, due to the tremendous cardiac reserve, the heart can deteriorate sometimes to one-fifth its normal pumping strength without any measurable evidence of cardiac failure. The cardiovascular regulatory process controlling the stroke volume and blood pressure 72 hours postirradiation as induced by epinephrine is still functioning very similar to that of the nonirradiated control animals. This was seen in the stroke work (left ventricular work output) which was very similar in all groups when the epinephrine-induced changes were expressed in percent of the preinjection level.

It is obvious that, in the terminal phase of the gastrointestinal radiation syndrome, the increased dehydration could rapidly deplete the cardiac reserve and further deteriorate the cardiovascular regulation. In this terminal phase some limiting factors could play a role in determining the length of the survival time. For example, the capacity of peripheral vasoconstriction is primarily important. The failure of fluid replacement at this time^{16,31} indicates that an irreversible state had already developed and the peripheral vascular collapse was inevitable. The persistent splanchnic ischemia, due to the increased vasoconstriction, might possibly initiate the release of a myocardial depressant factor after the 3rd day of irradiation. This factor was identified in a variety of shock states^{25,42} including intestinal ischemic shock²⁶ and presumably it decreases the myocardial capability for contraction. A recent experiment by Morgenstern et al.³³ apparently substantiates the role of both factors. They performed pancreatic duct ligation prior to 1500 rads of abdominal irradiation in dogs and the usual radiation sickness was prevented.

In conclusion, our study may add considerable support to Lushbaugh's concept³¹ that vascular alterations underlie the development of the so-called gastrointestinal radiation syndrome. Although at 48 hours postirradiation the major hemodynamic values were still unchanged, the cardiovascular regulation after epinephrine showed significant alterations. The mean blood pressure response was prolonged and the reflex bradycardia became less expressed. The epinephrine effect demonstrated that in the gastrointestinal radiation syndrome prior to the cardiovascular collapse a latent imbalance of alpha and beta adrenergic activity is already present. Further research is planned to determine the physiological and pharmacological significance

of this finding. These data indicate furthermore that the cardiovascular deterioration similar to other metabolically linked cardiovascular deteriorations^{17, 18} is peripheral rather than myocardial in origin.

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