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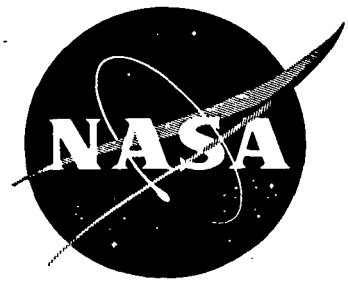

PULMONARY EDEMA AND PLASMA-VOLUME CHANGES IN DYSBARISM

A Thesis Presented to the
Faculty of the Graduate School of
The University of Texas Medical Branch at Galveston
in Partial Fulfillment of the
Requirements for the Degree of
Master of Arts

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

MANNED SPACECRAFT CENTER

HOUSTON, TEXAS 77058

PULMONARY EDEMA AND PLASMA-VOLUME CHANGES IN DYSBARISM

by

JAMES ALLEN JOKI, B.S.A.A.

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16. Abstract

Two groups of anesthetized, fasted pigs were utilized. One group of 13 animals (8.5 to 16.6 kilograms) was exposed to a high-pressure environment, and the other group of eight animals (6.9 to 20.0 kilograms) constituted the control group. The experimental group was subjected to an atmosphere of 90 percent nitrogen and 10 percent oxygen at a pressure of 50 psig for 30 minutes and then decompressed at a rate of 10 psi/min. Plasma volumes, using both iodine-125-tagged-albumin and chromium-51-tagged-cell dilution techniques, were measured before, immediately after, and at 30 and 60 minutes after decompression. Aortic and right-ventricular systolic pressures were also recorded. At 60 minutes after decompression, blood samples were taken; the animals were sacrificed; and the water content of of the lungs, kidneys, livers, and spleens was estimated by measuring tissue wet weight and dry weight. Protein extravasation and tissue blood volumes were determined by measuring the iodine-125-tagged-albumin and chromium-51-tagged-cell spaces in homogenates of the organs under investigation.

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INTRODUCTION

Inherent in the manned exploration of inner and outer space is the ever-threatening danger of debilitating decompression sickness. The etiology of decompression sickness has eluded precise definition, even though Robert Boyle in 1660 first noted its symptoms in animals that he subjected to reduced pressure. Boyle wrote the following after observing the effects of air rarefaction on small animals (ref. 1).

> Another suspition we should have entertain'd concerning the death of our Animals, namely, That upon the sudden removal of the wonted pressure of the ambient Air, the warm Blood of those Animals was brought to an Effervescence or Ebullition, or at least so vehmently expanded as to disturb the Circulation of the Blood, and so disorder the whole Oeconomy of the Body.

Boyle recognized that blood gases came out of solution and formed bubbles in blood vessels and in tissues. The occlusion of blood vessels in some manner

by these circulating bubbles has been the basis for interpretation of most decompression data.

Throughout the second half of the 17th century, the 18th century, and the early part of the 19th century, only a small number of persons were exposed to increased atmospheric pressures by the use of diving bells and early diving suits. However, physicians became aware of symptoms of decompression sickness soon after caissons were developed.

Caissons were successfully used in bridge building in 1839 by the French engineer, Triger. He reported a high incidence of pain in the extremities of men who returned to ambient pressure after a day's work within the pressurized environment of the caisson (ref. 2). These pains, aggravated by an erect position, resulted in a stooping posture that gave rise to the term "bends," the common designation of the disease. Caisson workers suffering from the bends often found relief by going back into the pressurized caisson. In 1847, two French physicians, Pol and Watelle (ref. 3), made the first serious study of this disease entity. They reported its symptoms to include joint and muscle pain, cramps, nausea and vomiting, unconsciousness, vertigo, double vision, dyspnea, chest pain, paralysis, and paresis. They pointed out that no symptoms of illness ever occurred when a man is under compression and that all illness occurred with decompression. They recognized the truth of the caisson worker's saying, "One only pays upon leaving." In 1872, Gal (ref. 4) reported that those muscles used most frequently by workers during their stay in compressed air were those in which pain most frequently occurred upon decompression. Alphores Jaminet (ref. 5),

medical supervisor for the first compressed-air works in the United States, strikingly reduced mortality and morbidity by reducing the duration of work, but he had nebulous ideas about the etiology of the disorder.

Paul Bert (ref. 6) was responsible for much of the early work on the pathogenesis of this disorder. He observed that nitrogen gas is dissolved in the blood and tissue fluids of experimental animals in proportion to the applied pressure and that this gas effervesces from the blood of animals and man if decompression is sufficiently rapid. Bert's contemporaries also observed bubbles in blood vessels when performing autopsies of victims of decompression sickness (refs. 7 and 8). These bubbles, it was suggested, gave rise to the symptoms of decompression sickness by blocking the capillaries and obstructing the blood supply (ref. 9). In vivo observations of intravascular bubbles after decompression have since been reported (refs. 10 to 12). Using frog-web and bat-wing models, Hill (ref. 13) observed bubbles flowing through capillaries after decompression from a pressure of 20 atmospheres. Recompression diminished the size of these bubbles and finally drove them back into solution. More recent observations in vivo have also verified the presence of bubbles in pial vessels of cats (ref. 14), in femoral venous circulation (ref. 15), and in the mesenteric microcirculation of dogs (ref. 16) after rapid decompression.

Bert not only observed intravascular bubbles after decompression from a compressed-air environment but also demonstrated that the bubbles were comprised primarily of nitrogen. He found that the illness that occurs upon

decompression was prevented by making the period of decompression sufficiently slow to allow time for the dissolved nitrogen to escape from the lungs.

Since 1660, it has been widely assumed that embolic nitrogen was the sole cause of pain (bends), pulmonary arteriolar blockage and edema ("chokes"), and neurocirculatory collapse ("staggers" and "itches"). However, numerous experimental findings suggest that the pathogenesis of decompression sickness is more complex (refs. 17 to 19). One of these findings is the severe diminution of plasma volume in decompression sickness of either high-altitude (refs. 20 to 22) or deep-sea-diving (refs. 23 to 25) origin. The resulting hypovolemia is severe enough to be a possible cause of circulatory shock, and, indeed, symptoms of circulatory shock do occur in these individuals. The efficacy of plasma expanders (6 percent dextran with a molecular weight of 40 000) in the therapy of decompression sickness (refs. 26 to 28) suggests that hypovolemia is a significant factor in the reported mortality and morbidity. Although the magnitude of plasma-volume loss has been measured in decompression sickness, little or no evidence is available to explain the mechanism or site of plasma-volume loss. Some of the plasma is apparently lost in pulmonary tissue. Histological evidence of pulmonary edema (refs. 17, 29, and 30) and pleural effusion (refs. 31 to 33) obtained from autopsies of human beings and experimental animals has been described in decompression sickness. Occasionally, survivors of rapid decompression have reported an abrupt onset of malaise accompanied by substernal distress; this distress is usually described as a burning sensation aggravated by deep inspiration that may provoke

paroxysmal coughing — the chokes. This syndrome is thought to be the subjective manifestation of a syndrome of labored breathing, pulmonary hypertension, and pulmonary edema that can be observed in experimental animals after decompression.

One might wonder if the plasma lost from vascular spaces in decompression sickness might not be accumulated primarily in pulmonary tissue, thus giving rise to the pulmonary edema. Unfortunately, no one has ever simultaneously measured the plasma-volume loss and the volume of fluid accumulation into the pulmonary tissue in order to test this hypothesis. The purpose of this study is to test the hypothesis that accumulated fluid in the lungs equals the amount lost from the vascular compartment.

METHODS AND MATERIALS

Experimental Protocol

Twenty-one immature hybrid swine, male and female, weighing 6.9 to 20.0 kilograms were randomly distributed between two groups. One group of 13 animals represented those that successfully completed the experimental protocol after being exposed to a high-pressure environment, and the other group of eight animals constituted the noncompressed control group. All animals were fasted for at least 12 hours before the experiment.

The animals were anesthetized by intraperitoneal injections of 6-percent sodium pentobarbital at a calculated dose of 40 mg/kg of body weight. Additional anesthetic was administered intravenously as necessary.

A tracheotomy was performed and a metal T-tube cannula was inserted to maintain a patent airway. Cutdowns were performed to allow cannulation of five vessels. One cannula was inserted into the external jugular vein and threaded into the right atrium for drug administration. Both femoral arteries were cannulated and the catheters threaded into the abdominal aorta. One of these catheters was used for pressure monitoring and the other for blood-sample withdrawal. Another cannula was inserted into the right atrium through the right femoral vein and was used to monitor central venous pressure. Another catheter, passed into the right ventricle through the left femoral vein, was used to monitor the right ventricular pressure. All five cannulas were Clay-Adams P. E. 200 polyethylene tubing and were initially filled with 0. 9-percent heparinized (3 units/ml) saline. After each sample withdrawal, the cannula employed was flushed with 2 milliliters of 0. 9-percent heparinized saline. Aortic, right-atrial, and right-ventricular pressures were monitored with Statham P23 strain gages and recorded on a Grass model 7 polygraph.

Thirty milliliters of blood were withdrawn during surgical preparation, tagged with chromium-51 (^{51}Cr) and subsequently reinjected into the animal for determination of red-cell mass. This technique is described in more detail in the section entitled "Analytical Techniques." Plasma volumes were ascertained indirectly both by the ^{51}Cr-tagged red cell and by iodine-125-tagged (^{125}I-tagged) albumin dilution techniques, as described by Wood and Levitt (ref. 34), Cleland and others (ref. 35), and Albert and others (ref. 36).

Before control blood samples were collected, all animals were heparinized with Liquamin at an initial dose of 3 units/ml of calculated blood volume. Subsequent hourly doses of 1 unit/ml of calculated blood volume were administered to prevent coagulation during blood-sample withdrawals.

After administration of tagged blood and heparin, aortic and right-ventricular pressures were allowed to return to preinjection values before control values were recorded.

Before compression, three sequential 10-minute arterial blood samples were collected for baseline hematocrit, plasma-volume, and red-cell-mass determinations. The animals were subjected to an atmosphere of 90 percent nitrogen and 10 percent oxygen at a pressure of 50 psig for 30 minutes and then decompressed at a rate of 10 psi/min in accordance with the compression-decompression schedule shown in figure 1. Additional series of blood samples were taken immediately after and at 30 and 60 minutes after decompression.

Approximately 90 minutes after decompression, the animals were sacrificed, and the lungs, kidneys, spleens, and livers were excised. The ratio of wet to dry weight and tissue homogenate activity for ^{51}Cr and ^{125}I were ascertained for these organs (ref. 37).

Analytical Techniques

Hematocrit. - The hematocrit of each sample was determined by centrifugation of duplicate capillary tubes for 3 minutes in a microhematocrit centrifuge (International model M. H.). These values were mathematically

corrected for plasma trapping as described by Albert and Albert (ref. 38) and Nadler and others (ref. 39).

Red-cell-mass and plasma-volume measurement by tagged dilution. - Red-cell mass was determined by the isotope-dilution principle, using ^{51}Cr-tagged cells (Abbott, sodium radiochromate).

During the initial surgery, 10 milliliters of blood were collected to determine the initial background plasma radioactivity in the ^{51}Cr energy spectrum. An additional 30 milliliters were collected and injected into an Abbott "safe tag" bottle containing 5 milliliters of acid citrate dextrose (ACD) solution (Abbott, special formula) and 100 microcuries of hexavalent ^{51}Cr. After 30 minutes of incubation in a water bath regulated at 37 $\pm$ 1° C, 50 milligrams of ascorbic acid were added to reduce any remaining unbound hexavalent chromium ions to the trivalent form and thus stop further red-cell tagging. This final step in the tagging procedure required an additional 15 minutes of incubation. Throughout the entire tagging procedure, the mixture was swirled at intervals to provide uniformity of tagging. Upon completion of tagging, 2-milliliter aliquots of the incubated blood were withdrawn for isotope counting. These samples served to establish the amount of ^{51}Cr activity injected into each animal. An aliquot of the remaining incubated red-cell mixture was centrifuged, and the ^{51}Cr activity of a 2-milliliter aliquot of the supernatant was determined. The ^{51}Cr activity found in this sample is assumed to be in the trivalent form as a result of the ascorbic-acid-induced oxidation and thus to bind to plasma proteins (ref. 40). This

plasma ^{51}Cr activity was therefore determined and taken into consideration in the calculation of plasma volume and red-cell mass (refs. 41 and 42).

The hematocrit of the incubated blood mixture was determined for later use in the calculation of red-cell mass according to the equation

$$\text{Blood-cell mass (volume)} = \frac{(\text{Number of cc injected})\left(\text{ACD} \times 100 - \{\text{SUP}[1 - (\text{ACD Hct} \times 0.96)]\}\right)(\text{Pt Hct})(0.915)(0.96)}{\text{WB} - \{\text{PL}[1 - (\text{Pt Hct})(0.96)]\}} \quad (1)$$

where ACD × 100 is counts/min at an aliquot taken from an ACD-tagged safe bottle, SUP is counts/min at an aliquot of supernatant taken from the ACD bottle, ACD Hct is the ACD-bottle hematocrit, Pt Hct is the animal hematocrit, WB is the counts/min at an aliquot of animal whole blood after isotope injection, PL is the counts/min at an aliquot of animal plasma after isotope injection, 0.96 is the correction factor for plasma trapping, and 0.915 is the correction factor for nonuniformity of red-blood-cell distribution.

After allowing a minimum of 20 minutes for these tagged cells to mix with the circulating blood, a sample of blood was withdrawn and centrifuged. The ^{51}Cr activities of both whole blood and supernatant were determined to establish red-cell mass. The techniques of assessing isotope concentration in these samples are described in the section entitled "Isotope Determination." Blood volume, and thus plasma volume, was calculated from the magnitude of the tagged-cell dilution and sample hematocrit.

Plasma volume measured by tagged-albumin dilution. - Plasma volumes were also determined by ^{125}I-tagged-albumin (Abbott, radio iodinated serum albumin) dilution. Before compression, a 2-milliliter sample of arterial

blood was collected to determine plasma background radioactivity in the energy spectrum to be used for ^{125}I-activity determination. After this sample collection, a dose of approximately 7 microcuries of ^{125}I-tagged albumin was injected into the right atrium via the external jugular-vein cannula. The cannula was immediately flushed with 4 milliliters of 0.9-percent heparinized saline to facilitate complete delivery of the dose. Arterial blood samples were withdrawn at 10, 20, and 30 minutes after the administration of the isotope. These blood samples were centrifuged about a 7-inch radius at 3000 rpm for 10 minutes, and a 1-milliliter aliquot of plasma from each was transferred to 16- by 100-millimeter tubes to be counted for ^{125}I activity. After isotope injection, the plasma ^{125}I-tagged-albumin concentration declined with time as a result of albumin extravasation. The concentration of ^{125}I-tagged albumin that would have existed at the time of injection if there had been complete mixing may be estimated by determining and correcting for the rate of albumin extravasation from the three sequential 10-minute arterial blood samples (refs. 8, 43, and 44).

A single syringe was utilized for isotope injection to facilitate uniformity in volume delivery and to reduce isotope-adsorption losses (ref. 45).

Compression-decompression procedure. - After the precompression blood sample was collected, the animals were placed in a Bethlehem N.B. 910 hyperbaric chamber and compressed in an atmosphere of 90 percent nitrogen and 10 percent oxygen to 50 psig (4.4 atmospheres absolute) at a rate of 10 psi/min. The chamber was continuously purged at a rate of 5 liters/min throughout the 30 minutes of compression to prevent buildup of

chamber carbon dioxide. After completion of the 30-minute sojourn at a simulated depth of approximately 100 feet of sea water, the chamber pressure was returned to ambient pressure at a rate of 10 psi/min. The total decompression time was 5 minutes. The complete compression-decompression schedule is outlined in figure 1. Immediately after decompression, the animals were removed from the chamber and prepared for blood-sample collection and blood-pressure measurements.

Post-mortem assays. - Approximately 90 minutes after decompression, the animals were sacrificed with the administration of 2 milliliters of sodium pentobarbital followed by 10 milliliters of saturated potassium chloride.

Immediately after death, the lungs, spleens, kidneys, and livers were rapidly excised from the animals. The major vessels of these organs were allowed to drain before weighing, as suggested by Guyton and Lindsey (ref. 46). Organ wet weights were measured on an Ohaus pan balance to the nearest 0.01 gram. Each of the organs studied was minced, placed in a Waring blender with two parts water by weight for each part of tissue, and homogenized for 10 minutes. Duplicate aliquots of tissue homogenants were weighed, and their ^{125}I and ^{51}Cr radioactivities were determined. These samples, with the remaining portions of the organ homogenates, were dried to a constant weight at 80° ± 5° C in a drying oven. They were initially weighed after 18 hours of drying and then reweighed at 4-hour intervals until no more than 0.05-gram decrease could be detected from the previous measurement. Organ wet-weight-to-dry-weight ratios were calculated to assess

water content, as described by Guyton and Lindsey (ref. 46), Levine and others (ref. 47), and Pearce and others (ref. 48).

Isotope determination. - A quantitative evaluation of the amount of activity for ^{51}Cr and ^{125}I in each tissue and blood sample was determined by counting radioactivity of the various samples in 15- to 40-keV and 240- to 340-keV spectrometric windows, respectively. Each window corresponds to a peak emission of the energy spectrum for that particular isotope. These counts, radioactive disintegrations, were recorded by a Baird Atomic Detector and corrected for background activity. Because each sample contained a mixture of both ^{51}Cr and ^{125}I, it was necessary to correct for the influence of each isotope upon the spectrometric window of the other. Mixed counts for each sample were converted to true counts by measuring the activity from the overlapping energy spectrum of each isotope in the spectrometric window of the other. From this calibration, the influence of the respective isotopes at each of the two spectrometric windows was calculated and used to null the effects of the overlapping energy spectra. The equations for the correction of overlapping energy spectra, as described by Wood and Levitt (ref. 34), are (given the isotopes ^{51}Cr and ^{125}I and the windows as just described and calibrating by counting each isotope in each window), for ^{51}Cr,

$$CTS_{15\text{-}40\ keV} - BKG_{15\text{-}40\ keV} = A \tag{2}$$

$$CTS_{240\text{-}340\ keV} - BKG_{240\text{-}340\ keV} = B \tag{3}$$

where CTS is the counts/min of specific calibration isotope and BKG is the background counts. Similarly, for ^{125}I,

$$CTS_{15\text{-}40\ keV} - BKG_{15\text{-}40\ keV} = C \tag{4}$$

$$CTS_{240\text{-}340\ keV} - BKG_{240\text{-}340\ keV} = D \tag{5}$$

The mix count MC is then calculated from the samples by

$$MC_{15\text{-}40\ keV} = \left(^{51}Cr + ^{125}I\right)_{15\text{-}40\ keV} - BKG_{15\text{-}40\ keV} \tag{6}$$

$$MC_{240\text{-}340\ keV} = \left(^{51}Cr + ^{125}I\right)_{240\text{-}340\ keV} - BKG_{240\text{-}340\ keV} \tag{7}$$

Finally, the true count TC is determined by

$$TC\left(^{125}I\right) = MC_{15\text{-}40\ keV} - (A/B)MC_{240\text{-}340\ keV} \tag{8}$$

$$TC\left(^{51}Cr\right) = MC_{240\text{-}340\ keV} - (D/C)MC_{15\text{-}40\ keV} \tag{9}$$

Statistical analysis. - The student's unpaired t-test was used to calculate levels of significance between the experimental and control groups in the investigation of organ edema, albumin extravasation, and erythrocyte congestion (ref. 49). The student's paired t-test was utilized whenever the animal served as its own precompression control. All values were considered statistically significant at or below the 0.05 level of probability ($p < 0.05$).

RESULTS

Thirteen out of 16 immature pigs successfully completed the experimental protocol after being subjected to an atmosphere of 90 percent nitrogen and 10 percent oxygen at a pressure of 50 psig for 30 minutes and then rapidly decompressed. After decompression, these animals exhibited cyanotic bluing of the oronasal mucous membranes, often had rapid (fig. 2) and irregular breathing, occasionally Cheyne-Stokes breathing, tachycardia (fig. 3), a fall in systemic arterial pressure (fig. 4), and a transitory right-ventricular systolic hypertension (fig. 5). The experimental data in this study reflect the data from those animals that successfully completed experimental protocol.

The post-mortem examination revealed bubbles in the right atrium and vena cava and gaseous distention of the gastrointestinal tract, while the kidneys, spleens, and livers appeared anatomically similar to the organs of the control pigs. The lower lobes of the lungs appeared plethoric, and a pink-tinged foam filled the bronchi, suggesting edema.

Plasma volumes were determined before compression and immediately after and at 30 and 60 minutes after decompression. These values, expressed as milliliters per kilogram of body weight, are presented in figure 6. Plasma volumes were calculated from ^{125}I-tagged-albumin dilution and from hematocrit and red-cell-mass values. Red-cell mass was determined by ^{51}Cr-tagged-red-cell dilution (fig. 7). Reductions in plasma volumes occurred in the experimental animals throughout the experiment

(fig. 6). One hour after decompression, plasma volumes determined by ^{125}I had declined by an average of 43 percent. This reduction represents a plasma-volume loss of 19 ml/kg of body weight. Similarly, a 15-percent reduction in plasma volume was found by the ^{51}Cr-hematocrit method. This change represents a plasma-volume reduction of 7 ml/kg of body weight. One hour after decompression, the plasma volumes of the experimental group, as determined by ^{51}Cr and ^{125}I methods, were significantly less ($p < 0.05$) than the plasma volumes of the control group. A slight, nonsignificant reduction in plasma volumes was observed in the animals of the control group at the time of sacrifice.

Hematocrits in the experimental group measured immediately after decompression had increased significantly ($p < 0.05$) over precompression values by an average of 6 percent. One hour after decompression, the hematocrit in the experimental group had increased 13 percent over precompression values and was significantly greater ($p < 0.05$) than the hematocrits of the control group (fig. 8). The hematocrits of the control group decreased nonsignificantly throughout the entire experiment.

Tissue-water measurements were determined by the ratio of organ wet weight to organ dry weight. The kidney, lung, spleen, and liver wet-weight-to-dry-weight ratios for the experimental and control groups are presented in tables I and II, respectively. The pulmonary wet weights and dry weights of the experimental group were both slightly greater than those of the control group. However, the pulmonary wet-weight-to-dry-weight ratio for the experimental group, sacrificed approximately 90 minutes after

decompression, was significantly greater ($p < 0.05$) than that of the noncompressed control group. The mean pulmonary water content of the compressed group at sacrifice was 4.32 ml/g of dry-tissue weight, and that of the control group was 4.00 ml/g of dry-tissue weight. This difference was significant ($p < 0.05$) and represents an increase of 0.74 ml/kg of body weight.

The kidney wet weights and dry weights of the experimental group were both slightly less than those of the control group (tables I and II). The kidney wet-weight-to-dry-weight ratio for the experimental group, however, was significantly less ($p < 0.05$) than the noncompressed control group. The mean kidney water content of the compressed group at sacrifice was 5.01 ml/g of dry-tissue weight, and that of the experimental group was 4.51 ml/g of dry-tissue weight. This difference was significant ($p < 0.05$) and represents a decrease of 0.48 ml/kg of body weight.

Pulmonary edema following decompression was anticipated, and it was thought that it might be attributed to pulmonary hypertension; consequently, the right-ventricular pressure was measured at preselected intervals throughout the experiment. These values were determined and compared to precompression values (fig. 5). Some of the pigs of the experimental group had surprisingly high right-ventricular systolic pressures before compression. Because this study was designed to observe the development of pulmonary hypertension, it was thought that these animals would be unsuitable; therefore, they were eliminated from this determination. The nine remaining pigs, each with a precompression right-ventricular systolic pressure of less than 40 mm Hg, had an average precompression right-ventricular

systolic pressure of 27 mm Hg. The change in the average right-ventricular systolic pressures of the nine remaining pigs is shown in figure 5. The right-ventricular systolic pressure 30 minutes after decompression was significantly greater ($p < 0.05$) than precompression values. This transitory change in the right-ventricular systolic pressure of the experimental group was not statistically different ($p < 0.05$) from the control group. The right-ventricular systolic pressure in the experimental group returned to normal 30 minutes later.

Immediately after decompression, the mean arterial pressures (systolic and diastolic) of both the experimental group and the control group were essentially unchanged from precompression values. Throughout the remainder of the experiment, the aortic pressures of the control group steadily decreased. One hour after decompression, both the experimental group and the control group exhibited significant decreases ($p < 0.05$) in aortic and diastolic pressures as compared to their respective precompression values (fig. 4). No statistically significant differences in aortic, systolic, or diastolic pressures were observed between the control group and the experimental group.

An index of albumin extravasation was obtained by measuring ^{125}I relative activity in the tissue homogenate (activity per gram dry weight of tissue per activity per milliliter of sacrifice blood) at post mortem. The activities in the tissue homogenates of the experimental and control groups for the spleens, kidneys, livers, and lungs are presented in tables III and IV, respectively. The ^{125}I-tagged-albumin concentrations of homogenates of

the four organs of the experimental group remained constant or increased (see p. 26). The lung, however, was the only tissue in which the difference between control and experimental tissue-homogenate ^{125}I relative activity was statistically significant ($p < 0.05$).

Chromium-51 relative activity in tissue homogenates (activity per gram dry weight of tissue per milliliter of blood at time of sacrifice) was used as an index of organ erythrocyte congestion. The activities in tissue homogenates from the experimental and control groups for the spleen, kidneys, liver, and lungs are presented in tables III and IV. Three of the four organs investigated (the liver, kidneys, and spleen) had lower relative ^{51}Cr activities and, consequently, lower red-blood-cell concentration per gram of tissue in experimental animals than in control animals. These relative differences were significant in the liver and spleen but not in the kidney. The relative ^{51}Cr activity of pulmonary tissue, however, was significantly greater ($p < 0.05$) in experimental animals than in control animals.

DISCUSSION

In this study, the experimental animals were subjected to an atmosphere of 90 percent nitrogen and 10 percent oxygen at a pressure of 50 psig for 30 minutes and then rapidly decompressed. This moderately severe exposure produced an $L.D._{20}$ for these animals. In this environment, the animals were exposed to an oxygen partial pressure of 335 mm Hg. This exposure is unlikely to produce any symptoms of oxygen toxicity. Oxygen toxicity is dependent upon the oxygen partial pressure and duration of

exposure. Oxygen partial pressures of 500 mm Hg have been tolerated by human beings for 100 hours without their suffering measurable ill effects (ref. 50). This and other studies suggest that an oxygen partial pressure of 335 mm Hg is insufficient for the development of oxygen-toxicity symptoms even with longer exposures than those employed in these experiments (refs. 37 and 51).

Current evidence suggests that the plasma-volume reduction of dysbarism may be a direct consequence of pulmonary-edema formation. The object of this study was to measure and correlate the plasma fluid losses with pulmonary-water transudation and to investigate possible causes of plasma reduction in decompression sickness. In addition to plasma-water extravasation, albumin transudation and erythrocyte congestion accompanying decompression sickness have been reported (refs. 30, 52, and 53). In this investigation, significant plasma reductions, evidence of increased pulmonary water, albumin, and erythrocyte content occurred after decompression. This study also indicated a reduction of water and erythrocyte content in the kidney and a significant reduction of erythrocyte content in both the liver and the spleen after decompression.

Plasma Volume

After decompression, a substantial reduction in plasma volume was found, as has been reported by several previous investigators (refs. 33, 53, and 54). These volumes were measured by ^{125}I-tagged-albumin dilution and by measurement of red-cell-mass ^{51}Cr-tagged-cell dilution with a

correction for hematocrit. Both techniques were used because each alone could yield questionable results. Previous studies have indicated increased albumin extravasation after decompression (ref. 43). Consequently, ^{125}I-tagged-albumin studies, if used alone, might be questioned on the grounds that the volume of the albumin space might be larger than the plasma space. Plasma volumes determined by ^{51}Cr-tagged-cell dilution might be questioned because of cell sequestration and release. The volume measured by these two techniques yielded two sets of results that varied slightly from each other. Similar differences have been reported by numerous investigators (refs. 55 and 56). Many investigators have reported plasma volumes determined from albumin dilution to be 10 to 25 percent greater than those calculated from red-cell mass and hematocrit (refs. 57 and 58). These differences have been attributed to the differences in hematocrits between the large and small vessels (refs. 55 and 59). It is common practice to use a correction factor, the ratio of body hematocrit to large vessel hematocrit, or "F" ratio, to compensate for the uneven red-cell distribution (refs. 39 and 41).

Plasma volumes were calculated before compression and immediately after and at 30 and 60 minutes after decompression. Mean precompression plasma volumes of 46 ml/kg of body weight by ^{125}I dilution and of 41 ml/kg of body weight by red-cell-mass/hematocrit were determined.

One hour after decompression, plasma volumes, determined by ^{125}I dilution, declined significantly ($p < 0.05$) by an average of 43 percent to

27 ml/kg of body weight. A reduction of 15 percent was observed in the ^{51}Cr-hematocrit plasma-volume determination.

The plasma-volume reductions noted in this study may appear surprisingly large; however, reductions of a similar magnitude have previously been observed in experimental animals (refs. 53, 60, and 61) and in man (refs. 27, 54, and 62) with decompression sickness. Cockett and Nakamura (ref. 27), utilizing the same isotope-dilution technique used in this study, elicited plasma deficits of 20 to 32 percent within 3 hours after decompression. Cockett and Nakamura's animals were subjected to a compression pressure of 74 psig for 60 minutes and then decompressed at 7 psi/min. Brunner and others (ref. 54) measured similar plasma-volume reductions in human subjects with decompression sickness and suggested that the circulatory shock found in these men resulted from the diminution in plasma volume.

Hemoconcentration was also observed in the experimental animals after decompression (fig. 8). Some hemoconcentration is a consequence of the reduced plasma volume. However, the possible role of splenic discharge of red cells upon hematocrit alteration must be considered (refs. 56, 57, and 63). Many investigators, working with sodium-pentobarbital-anesthetized dogs, have reported splenic engorgement that might markedly influence hematocrit (refs. 56, 64, and 65). Hahn and others (ref. 66) produced a substantial increase in hematocrit by injecting epinephrine in nebutalized dogs but were unable to find a corresponding change in red-cell mass as measured by tagged-red-cell dilution. These results indicated

either that there was a rapid equilibration of tagged red cells between circulating blood and within the sequestering organs or that there is a minimal splenic discharge of cells. The possibility of splenic discharge of cells in decompression sickness is reinforced by Reeve and others (ref. 67) and by Cockett and Nakamura (ref. 53). They observed greater hematocrit rises in nonsplenectomized dogs than in similar animals that had been splenectomized 2 to 4 weeks before being subjected to decompression stress. In the current study, an increase in hematocrit (fig. 8) and a relatively constant red-cell mass (fig. 7) were found. These findings favor the interpretation that the hematocrit increase resulted largely from the plasma-volume reduction and not from red-blood-cell release from splenic stores. The possible causes of this plasma-volume reduction will be discussed subsequently.

Tissue-Fluid Measurements

Although substantial evidence exists of a serious plasma extravasation in decompression sickness, there is little evidence of the relative magnitudes of fluid uptake in various tissues. Histological evidence of pulmonary edema (refs. 68 to 70) and pleural effusion (refs. 23, 30, and 71) obtained from autopsies of human beings and experimental animals with decompression sickness suggest that much of the plasma was lost into the pulmonary tissue. Cerebral edema has also been observed, but otherwise there is little evidence of fluid uptake by other tissue (refs. 30 and 33).

In this study, tissue-water volumes were estimated in various tissues by measuring the ratio of organ wet weight to organ dry weight. This ratio

is preferable to an organ-wet-weight-to-body-weight ratio, at least for pulmonary tissue (ref. 46). In the lung, the blood wet-weight-to-dry-weight ratio is approximately the same as the normal lung wet-weight-to-dry-weight ratio. Consequently, vascular congestion has relatively little effect on tissue wet-weight-to-dry-weight ratio but does affect organ-wet-weight-to-body-weight ratio. Tissue edema increases the organ wet-weight-to-dry-weight ratio.

In this investigation, the pulmonary wet-weight-to-dry-weight ratio (5.32 $\pm$ 0.05 S.E.M.) for the group with experimental dysbarism was significantly greater ($p < 0.05$) than that of the noncompressed control group (5.00 $\pm$ 0.07 S.E.M.), indicating a fluid-volume increase from 4.00 to 4.32 ml/g of tissue dry weight. This represents an increase in lung water of 0.74 ml/kg of body weight and accounts for approximately 4-percent, based upon ^{125}I, and 11-percent, based upon ^{51}Cr, measures of the plasma deficit in the animals (fig. 9). It is believed that these pulmonary wet-weight-to-dry-weight ratios indicated pulmonary edema in decompression sickness. As pointed out before, pulmonary edema has been observed by histological studies in decompression sickness.

Tissue-Congestion Measurements

In an attempt to verify vascular congestion in decompression sickness that has been reported in the literature, red-blood-cell space was measured in tissue by determining the ratio of ^{51}Cr activity per gram of dry tissue to that of blood at the time of sacrifice (fig. 10). In the lung, there was a

23 percent greater ^{51}Cr space in the pulmonary tissues of decompressed animals than in those of the control animals. These findings indicated a corresponding 23-percent difference in red-cell concentration per gram of dry pulmonary tissue and suggest either an increase in pulmonary blood volume or an increase in the hematocrit of blood within pulmonary tissue.

Pulmonary blood volume was also estimated by measuring ^{125}I activity per gram of dry pulmonary-tissue weight and comparing these values to the ^{125}I activity of venous blood.

$$\text{ml/g of dry pulmonary tissue} = \frac{\text{lung counts/g of dry pulmonary tissue}}{\text{plasma counts/ml blood}} \tag{10}$$

The values thus obtained are valid estimates of blood volumes only if the albumin space of tissue is equal to its plasma space. The pulmonary blood volume of decompressed animals measured by ^{125}I dilution was 30 percent larger than control animals, while that measured by ^{51}Cr was, on the average, 23 percent greater (fig. 10). Both measurements suggest substantial blood pooling in pulmonary tissue in decompression sickness. Pulmonary congestion has previously been reported from autopsies and histological studies of decompressed animals and human beings (refs. 32, 33, and 52). The difference between the ^{51}Cr and ^{125}I measurements is interpreted as an indication of a greater rate of albumin extravasation in decompressed animals than in control animals. Increased albumin extravasation, measured by a different technique, has previously been reported in decompressed dogs (ref. 43).

The wet-weight-to-dry-weight ratios of the kidneys, livers, and spleens of the decompressed and control groups were studied in an effort to identify additional sites of plasma extravasation. These ratios were 4.55 ± 0.20 S.E.M. and 4.54 ± 0.06 S.E.M., respectively, for the livers and spleens of the control animals and 4.56 ± 0.07 S.E.M. and 4.58 ± 0.05 S.E.M. for the corresponding tissues of the decompressed animals. These differences were not statistically significant ($p < 0.05$).

In the kidneys, the mean tissue wet-weight-to-dry-weight ratios for the decompressed animals (5.51 ± 0.12 S.E.M.) were significantly less ($p < 0.05$) than those of the control group (6.01 ± 0.11 S.E.M.). This decrease from 5.01 to 4.51 ml/g of tissue dry weight represents a 0.48-ml/kg of body weight reduction in renal fluid (fig. 9). The reason for this difference is not evident. However, the kidney, when perfused under normal arterial pressure, has a remarkably large interstitial volume that comprises 30 to 50 percent of the volume of the organ (refs. 72 to 74). When perfusion pressure is decreased, a large percentage of these fluids normally drains from the organ. Perhaps the more precipitous reduction in arterial pressures observed after decompression (fig. 4) are related to the lower renal volumes observed in the decompressed group.

To estimate vascular congestion in various visceral organs, the ^{51}Cr-tagged-cell space of liver, spleen, and kidney was measured. In all instances, the ^{51}Cr space was lower in the decompressed group than in the control group (fig. 10). This difference in the kidney tissue was not significant. Changes in spleen and liver represent decreases of 2.89 milliliters

of blood per kilogram of body weight and 0.15 milliliters of blood per kilogram of body weight in the liver and spleen, respectively (fig. 10). Both tissues are known to serve as red-cell stores. These data are suggestive that release of red blood cells into the circulation occurred in spite of the fact that data reported earlier in this study indicated that this was not the major cause of elevation in hematocrit. Conversely, ^{125}I space in the liver remained constant, was not significantly increased in the kidney, and was substantially elevated in the spleen (fig. 10). If both ^{51}Cr-tagged cells and ^{125}I-tagged albumin were limited to the vascular space, their measurement would have given an estimate of blood volume. Because there was a reduction in ^{51}Cr space in all of these organs, it is believed that the difference in the ^{125}I and ^{51}Cr values indicated an accelerated extravasation of ^{125}I-tagged albumin in the animals subjected to decompression.

The tissue-water contents calculated from pulmonary, splenic, hepatic, and renal wet-weight-to-dry-weight-ratio studies failed to account for a significant fraction of the measured plasma extravasation. However, the pulmonary-water transudation that was observed was sufficient to produce a moderate case of pulmonary edema (an approximate increase in organ weight by 10 percent). Several mechanisms could be responsible for pulmonary-edema formation in decompression sickness. Among these are elevations in capillary hydrostatic pressure, increased capillary permeability, and decreased lymphatic drainage. One of the objects of this study was to determine which of these mechanisms has a primary role.

Elevated capillary hydrostatic pressure, when present, will result in the development of pulmonary edema (refs. 75 and 76). Staub and Storey (ref. 77) and Said and others (ref. 78) reported that increased pulmonary vascular volume and pulmonary edema are produced by infusion of sufficient blood or dextran to increase left-ventricular end diastolic pressure. Gruhzit and others (ref. 75) induced pulmonary edema, measured by wet-weight-to-dry-weight ratio, by partial constriction of the aorta with consequent elevation of left-atrial pressure. They observed fluid transudation into the lungs when the left-atrial pressure exceeded the estimated colloid osmotic pressure of the perfusing plasma. The rate of pulmonary-edema formation was directly proportional to mean left-atrial pressure above the estimated colloid osmotic pressure of 25 mm Hg. Niden and Aviado (ref. 79) induced pulmonary hypertension by glass-bead injection into the right ventricle and observed tachypnea, bradycardia, and fall in aortic pressure; these are characteristic symptoms of decompression sickness (refs. 15, 26, and 80). All these investigators implied that the observed pulmonary edema was associated with elevations of pulmonary capillary hydrostatic pressure. In some circumstances, elevations in pulmonary arterial pressures also result in elevations in pulmonary capillary hydrostatic pressure (refs. 15, 81, and 82).

Although pulmonary capillary pressure was not measured, the right-ventricular systolic pressure was monitored and used as an index for pulmonary arterial hypertension. Four of the 13 animals had pulmonary systolic pressures of more than 40 mm Hg before compression. Analyses of the remaining nine animals indicated that immediately after

decompression, the right-ventricular pressure increased to 33 mm Hg, a 21 percent rise. Thirty minutes later, it had risen to an average of 51 mm Hg pressure, which was significantly greater ($p < 0.05$) than the precompression value of 27 mm Hg. At the 60-minute measurement, the right-ventricular pressure had returned to the precompression values. These findings indicate that a transitory pulmonary hypertension occurred in the animals. Similar increases, transient but large, in pulmonary arterial pressures have been observed in animals during decompression sickness (refs. 83 to 85).

It has been suggested that these pulmonary hypertensive responses could result from vasoconstriction (refs. 82 and 86), mechanical blockage of the vasculature (refs. 52, 87, and 88), or altered hemodynamics (refs. 19 and 49).

Evidence exists that serotonin, through its vasoactive properties, may be involved in the pulmonary hypertension of decompression (refs. 89 and 90). Kahn and others (ref. 91) and Stein and others (ref. 92) observed an increase in total pulmonary resistance after experimental intravenous air injection. The elevated pulmonary resistance was prevented by rendering the animals thrombocytopenic (refs. 24, 89, and 90) and by infusing a serotonin antagonist, methysergide (ref. 81). Kahn also reported that he was unable to elicit the pulmonary hypertension in platelet-deficient animals upon intravenous air injections. Both Kahn and Stein attributed the increase in pulmonary resistance after the injection of the air bolus to the release of serotonin from platelets. Daicoff and others (ref. 81) reported that

extremely small doses of exogenous serotonin intravenously produced a transient rise in pulmonary arterial pressure, intrapulmonary venous pressure, and left-atrial pressure. With intravenous administration of autologous blood clots, Daicoff produced a significant pulmonary hypertension without altering systemic arterial pressure or cardiac output. There was no difference in the serotonin concentration of arterial blood before and after embolization; however, the serotonin concentration increased markedly in the impacted pulmonary emboli when compared to clots before embolization (ref. 81). Philip and Gowdey (ref. 89) observed a substantial increase in the mortality rate of serotonin-pretreated rats after decompression.

Pulmonary hypertension from mechanical blockage of the vasculature may be induced by emboli of sufficient size. Several investigators have reported embolism originating from lipids (refs. 13 and 93), bubbles (refs. 53 and 94), or aggregates of formed elements of blood (refs. 33 and 95) in decompressed animals. The predominant localization of these emboli in the pulmonary vessels after decompression has been observed in both man (refs. 6 and 69) and experimental animals (refs. 52, 53, and 91). Anatomically, the lung is presumed to be the primary site of embolism because it provides the first capillary bed to be encountered by emboli in the systemic venous return (refs. 96 to 98). The pulmonary vasculature also might be suspected of being more susceptible to bubble embolization than systemic vasculature because of its lower perfusion pressure. Under sufficient pressure, bubbles, which might deform, or massed bubbles, friable enough to break apart, could pass through the systemic capillaries and become embolic

under the lower perfusion pressure of the pulmonary circuit (ref. 99). Intra-arterial injection of hypertonic saline, glucose, or radio-opaque agents causes transitory red-cell-aggregation formation, pulmonary hypertension from occlusion of pulmonary vessels, and a drop in aortic pressure (refs. 100 to 102). These studies revealed passage of red-cell aggregates through systemic capillaries coincident with pulmonary vascular occlusion. Durant and others (ref. 87) calculated that a pressure of 150 mm Hg was necessary to force bubbles through a 10-micron rigid-fluid-walled capillary.

The possibility that pulmonary air emboli in decompression sickness may increase vascular resistance is reinforced by the observation that the appearance of venous bubbles preceded the pulmonary hypertension after decompression (refs. 15 and 84). After rapid decompression from 130 psi, Durant and others (ref. 87) found bubbles in all major vessels and heart chambers, but predominantly in the vena cava, right ventricle, and pulmonary artery. He concluded, from the relative paucity of bubbles in the pulmonary veins and left heart, that it was difficult under normal physiological conditions for gaseous emboli to pass through the pulmonary circuit. Bubbles in the pulmonary arteries are a consistent finding in post-mortem examinations of animals with experimental decompression sickness (refs. 11, 52, and 53). Heimbecker and others (ref. 29), studying animals dying of decompression, reported a serious impairment of blood flow to vital tissues, presumably caused by gas emboli, and concluded that this was the immediate cause of death. Intravascular bubbles have also been observed in vivo after decompression (refs. 15, 84, and 85). Further, after decompression,

bubbles have been observed in plastic viewing chambers in the femoral venous circulation before the onset of pulmonary hypertension (refs. 15 and 84). Upon subsequent recompression, pulmonary pressures returned to normal, and bubbles in the blood flowing through the chamber were either no longer visible or were markedly reduced in size.

Although the presence of intravascular bubbles and the reversibility of the pulmonary hypertension with increased barometric pressure indicates that the bubbles located in the pulmonary vasculature may be responsible for increased pulmonary vasculature resistance, other types of emboli must be considered. Pulmonary fat emboli have been observed in decompression sickness by several investigators (refs. 23, 32, and 52). Although some of these emboli have been found to contain myeloid tissue (ref. 33), indicating bone marrow as their source, adipose tissue and plasma lipid coalescence have been suggested as major sources of these emboli (refs. 103 and 104). Lehmen and Moore (ref. 105) reported that insufficient myeloid tissue exists in the marrow to account for the total fat present in the lungs of patients who succumbed to fat embolism after trauma. Furthermore, the fat emboli of decompressed rabbits were found to contain a high concentration of cholesterol (ref. 98). Marrow and adipose fat contain less than 1 percent cholesterol, while serum lipo-proteins contain 10 to 40 percent cholesterol (ref. 98). These findings suggest that depot fat and marrow contribute little to the formation of fat emboli and that they result from coalescence of circulating plasma lipids (ref. 106). Heparin has been found to reduce significantly the mortality of decompression sickness in rats (refs. 103 and 107).

LeQuire and others (ref. 98), Philip (ref. 104), and Reeves and Workman (ref. 108) suggested that the benefits of heparin result, at least in part, from its antilipemic properties.

Platelet aggregates have been found in pulmonary vessels in decompressed animals (ref. 90) and may constitute yet another form of pulmonary embolism. Jacobs and Stewart (ref. 93) have observed that platelet aggregates form around intravascular bubbles in decompressed rats and that these later appeared as free aggregates, which, they felt, could occlude fine vessels. Furthermore, a reduction in circulating platelets (ref. 90), an increased platelet adhesiveness (ref. 109), and an accelerated blood clotting (ref. 103) have also been observed in decompressed animals. Philip and Gowdey (ref. 89) reported that severe decompression sickness in rats was accompanied by thrombocytopenia in conjunction with reduced plasma lipids. They reported that, during intravenous air infusion, the decrease in circulating platelet count was exaggerated by serotonin and adenosine diphosphate and was retarded somewhat by adenosine. Philip and Gowdey (ref. 89) and Lambertsen (ref. 110) suggested that, in severe decompression sickness, microthrombi involving platelet aggregates may occur in a manner similar to that seen in disseminated intravascular coagulation (DIC). Reductions in partial thromboplastin times have also been observed in dogs with decompression sickness and were suggested as a possible indication of DIC (ref. 111).

Reduction in systemic microcirculatory flow with marked red-cell-aggregate formation has also been observed after several types of trauma

(refs. 13, 68, and 83). After decompression, severe depression in capillary flow accompanied by red-cell aggregation has been reported in the cheeks of hamsters (ref. 112), pial circulation of cats (ref. 113), and in mesenteric microcirculation of dogs (ref. 114). These findings suggest that similar changes might occur in the pulmonary circuit and contribute to the pulmonary hypertension and increased blood-flow impedance of the pulmonary circuit after decompression. Elevation in blood viscosity, which would impede pulmonary perfusion, has also been observed in decompression sickness. This viscosity increase has been suggested to result, at least in part, from increased red-cell-aggregate formation and also from the increased hematocrit observed after decompression (refs. 43, 51, and 69).

Derangement in lymphatic runoff could result in pulmonary edema. A buildup of ^{125}I activity in tissue homogenates, as found in this study (fig. 10), would occur with lymphatic blockage. However, it appears unlikely that a simple lymphatic obstruction was the primary cause of the pulmonary edema observed. Visscher and others (ref. 115), working with dogs of similar weight, calculated that a moderate case of edema (10 percent increase in tissue net weight) would require 6 hours of lymphatic obstruction. Although lymphatic obstruction might possibly produce a more rapid pulmonary edema in pigs, a direct measure of pulmonary lymph flow would be necessary to establish the possibility.

Alteration in vascular permeability is another cause of pulmonary edema. Serotonin or histamine applied topically to minute vessels induced increased leakage from pulmonary capillaries of intravenously injected

colloid carbon particles without alterations in the caliber of these vessels (ref. 86). These findings suggest that serotonin and histamine increased vascular permeability by a direct effect upon the endothelial cells or their junctions. An additional substance, smooth muscle activating factor (SMAF), is thought by some to be involved in pulmonary vascular permeability changes in decompression sickness (ref. 115). Intradermally injected SMAF has been reported to increase the vascular transudation of injected pontamine blue, as indicated by bluing of rabbit skin. Activity of SMAF has been found to be significantly greater in the lungs of decompressed animals than in those of control animals. The effects of bradykinin and histamine on vascular permeability are reported to be potentiated by SMAF (refs. 116 and 117). Yet another line of evidence that permeability plays a role in some form of pulmonary edema is to be found in the work of Staub and Storey (ref. 77) and Singer and others (ref. 88). They produced diffuse bilateral pulmonary edema, as indicated by histological studies, by unilobar miliary-starch embolization and by intravascular injection of alloxan, in absence of a critical rise in pulmonary capillary hydrostatic pressure.

The increased albumin extravasation after decompression found in this study is suggestive of an increase in pulmonary vascular permeability. In decompressed animals, the pulmonary ^{125}I-tagged-albumin space was 23 percent greater than the corresponding ^{51}Cr-tagged-cell space, while the ^{125}I space of the control animals was only 16 percent greater than the corresponding ^{51}Cr space. This may be interpreted as an indication of substantially greater albumin extravasation in decompression.

CONCLUDING REMARKS

The loss of plasma during decompression sickness may be primarily into the pulmonary space. This study was designed to test this hypothesis.

Two groups of anesthetized, fasted pigs were utilized. One group of 13 animals (8.5 to 16.6 kilograms) was exposed to a high-pressure environment, and the other group of eight animals (6.9 to 20.0 kilograms) constituted the control group. The experimental group was subjected to an atmosphere of 90 percent nitrogen and 10 percent oxygen at a pressure of 50 psig for 30 minutes and then decompressed at a rate of 10 psi/min.

Plasma volumes, using both iodine-125-tagged-albumin and chromium-51-tagged-cell dilution techniques, were measured before, immediately after, and at 30 and 60 minutes after decompression. Aortic and right-ventricular systolic pressures were also recorded. At 60 minutes after decompression, blood samples were taken; the animals were sacrificed; and the water content of the lungs, kidneys, livers, and spleens was estimated by measuring tissue wet weight and dry weight. Protein extravasation and tissue blood volumes were determined by measuring the iodine-125-tagged-albumin and chromium-51-tagged-cell spaces in homogenates of the organs under investigation.

Transient elevations in right-ventricular systolic pressures, severe plasma-volume reductions, and moderate pulmonary edema developed in the experimental animals after decompression. Only minor, nonsignificant differences were found in tissue-water contents of the livers and spleens of

decompressed and control animals. Tissue-water contents of the kidneys of decompressed animals were significantly lower than those of the control group. The increased volume of pulmonary water of decompressed animals as compared to control animals indicated a pulmonary-water retention in decompression sickness, which accounted for 4 to 11 percent of the plasma loss measured by iodine-125 and chromium-51, respectively. The observed increase in right-ventricular systolic pressures suggests the presence of pulmonary hypertension as a possible cause of the observed pulmonary edema.

The pulmonary blood volume of decompressed animals measured by iodine-125 dilution was 30 percent larger than in control animals, while that measured by chromium-51 was on the average 23 percent greater. In addition, there was a reduction in chromium-51 space in liver, kidney, and spleen, despite a relatively constant increase in iodine-125 space. These differences are believed to indicate an accelerated extravasation of iodine-125-tagged albumin in the animals subjected to decompression.

This study has demonstrated a greater proportionate plasma loss into the pulmonary space than the plasmic loss from capillaries of liver, spleen, and kidney. However, the magnitude of this loss from pulmonary capillaries is not sufficient to account for the total observed reduction in plasma volume.

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TABLE I. - EXPERIMENTAL-GROUP TISSUE WEIGHTS (50 psig at 30 min)

Animal no./ statistical parameter	Body weight, kg	Kidney			Liver			Lung			Spleen		
		Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry
1	10.6	9.89	60.30	5.79	75.19	345.30	4.58	28.13	146.28	5.20	4.54	21.19	4.68
2	11.2	9.90	49.60	4.76	76.29	343.67	4.51	29.07	153.78	5.29	4.14	19.15	4.64
3	8.6	16.98	81.28	4.57	90.13	424.01	4.70	26.46	134.42	5.08	5.17	24.71	4.78
4	11.6	11.54	66.52	5.88	80.18	377.66	4.71	27.88	146.93	5.27	5.02	22.94	4.57
5	14.1	10.76	60.93	5.78	72.05	317.02	4.40	35.87	189.39	5.28	6.31	29.40	4.66
6	12.4	12.31	68.66	5.66	101.39	439.74	4.34	30.32	154.03	5.08	4.59	20.73	4.39
7	10.3	11.28	59.21	5.25	76.51	317.98	4.83	31.05	158.36	5.10	5.26	24.52	4.66
8	14.7	11.89	67.40	5.67	90.50	396.44	4.38	25.77	145.60	5.65	4.63	20.72	4.48
9	16.7	7.50	41.44	5.53	61.13	254.22	4.18	28.63	159.47	5.57	2.52	10.44	4.11
10	8.4	12.29	74.85	6.04	132.25	549.20	4.16	32.15	168.47	5.24	5.57	25.57	4.60
11	15.3	16.32	94.08	5.77	97.16	471.32	4.85	31.89	171.89	5.39	6.27	30.47	4.86
12	14.8	11.18	60.78	5.44	73.99	348.57	4.71	26.85	145.53	5.42	4.07	18.84	4.63
13	13.1	14.82	81.44	5.50	91.56	446.01	4.88	29.45	163.74	5.56	5.70	25.93	4.55
Number	13	13	13	13	13	13	13	13	13	13	13	13	13
Mean	12.64	12.46	68.63	5.51	87.94	401.02	4.56	29.50	156.94	5.32	5.24	24.00	4.58
Standard deviation	2.62	2.65	15.34	.43	17.85	81.44	.25	3.91	21.59	.19	1.36	7.18	.19
Standard error	.65	.71	4.10	.12	4.77	21.77	.07	1.05	5.77	.05	.36	1.92	.05
Distribution	--	--	3.22	--	--	0.04	--	--	3.61	--	--	0.56	--
Probability	--	--	<0.05	--	--	>0.05	--	--	<0.05	--	--	>0.05	--

TABLE II. - CONTROL-GROUP TISSUE WEIGHTS

Animal no./ statistical parameter	Body weight, kg	Kidney			Liver			Lung			Spleen		
		Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry	Dry, g	Wet, g	Wet/dry
1	14.1	12.72	76.37	6.15	123.08	391.74	3.19	36.85	178.10	4.83	6.44	28.75	4.46
2	8.9	8.95	50.90	5.69	70.36	324.22	4.61	20.32	107.08	5.03	4.13	19.68	4.77
3	14.9	12.21	74.77	6.12	114.04	515.17	4.52	28.13	156.87	5.03	6.17	26.97	4.37
4	10.8	10.43	65.29	6.26	64.23	301.64	4.70	32.48	170.20	5.24	3.88	17.85	4.60
5	20.0	20.25	119.35	5.89	124.78	585.12	4.69	37.09	189.20	5.04	9.33	41.20	4.42
6	6.9	7.98	48.46	6.07	50.51	254.27	5.03	18.91	96.18	5.09	2.77	11.82	4.27
7	15.4	16.75	97.10	5.80	116.54	549.81	4.72	37.37	171.33	4.59	6.99	33.11	4.74
8	14.0	15.13	99.28	6.56	86.98	429.28	4.94	30.62	158.13	5.16	7.28	33.98	4.67
Number	8	8	8	8	8	8	8	8	8	8	8	8	8
Mean	13.13	12.93	77.76	6.01	89.78	408.49	4.55	28.68	143.40	5.00	5.61	25.48	4.54
Standard deviation	4.13	3.88	23.46	.33	28.37	118.59	.58	7.91	35.85	.21	2.19	9.74	.18
Standard error	1.46	1.29	7.82	.11	9.46	39.53	.20	2.64	11.95	.07	.73	3.25	.06

TABLE III.- EXPERIMENTAL-GROUP (50 psig at 30 min) ISOTOPE ACTIVITY

[Isotope activity per gram dry weight of tissue/activity per milliliter of sacrificed blood]

Animal no./ statistical parameter	Kidney		Liver		Lung		Spleen	
	^{51}Cr	^{125}I	^{51}Cr	^{125}I	^{51}Cr	^{125}I	^{51}Cr	^{125}I
1	0.406	1.241	0.555	2.228	1.280	1.258	0.929	0.451
2	.624	1.178	.619	1.807	1.272	1.886	.773	1.002
3	.356	1.153	.336	1.651	1.282	1.290	.951	1.195
4	.377	1.416	.627	1.587	1.706	1.226	1.171	.505
5	.500	1.077	.936	1.504	1.314	2.513	1.118	.625
6	.701	1.310	.699	1.230	1.349	1.743	1.209	1.725
7	.762	.998	.578	2.043	1.486	1.510	.601	.736
8	.833	.661	.251	1.353	1.664	1.831	1.089	.411
9	.304	.971	.525	1.625	1.360	1.936	2.316	.770
10	.369	.704	.549	1.690	1.440	1.941	.743	.630
11	.701	.937	.482	2.485	1.221	1.478	.913	1.114
12	.659	1.088	1.192	2.762	1.321	1.606	.982	.600
13	5.01	1.064	.739	1.732	1.281	1.845	.706	.913
Number	13	13	13	13	13	13	13	13
Mean	0.546	1.0614	0.619	1.825	1.383	1.697	1.039	0.821
Standard deviation	.177	.216	.243	.443	.152	.357	.427	.353
Standard error	.051	.060	.067	.128	.042	.099	.118	.098
Distribution	.375	.1638	3.15	.01	3.468	2.53	2.00	1.40
Probability	>0.05	>0.05	<0.05	>0.05	<0.05	<0.055	<0.05	>0.05

TABLE IV.- CONTROL-GROUP ISOTOPE ACTIVITY

[Isotope activity per gram dry weight of tissue/activity per milliliter of sacrificed blood]

Animal no./ statistical parameter	Kidney		Liver		Lung		Spleen	
	^{51}Cr	^{125}I	^{51}Cr	^{125}I	^{51}Cr	^{125}I	^{51}Cr	^{125}I
1	0.769	1.191	0.663	1.901	0.936	0.990	1.507	0.942
2	.415	1.469	.692	1.963	1.173	1.187	1.861	.626
3	.568	.898	1.550	1.991	1.343	1.894	1.515	.605
4	.494	.831	1.250	1.631	1.232	1.654	1.570	.544
5	.501	.889	.995	1.733	1.178	1.374	1.433	.684
6	.679	1.116	.626	1.043	.744	.942	1.055	.413
7	.582	1.112	1.451	1.577	1.055	1.057	1.041	.774
8	.572	.859	1.030	2.022	1.281	1.312	1.150	.417
Number	8	8	8	8	8	8	8	8
Mean	0.573	1.045	1.032	1.826	1.118	1.301	1.392	0.626
Standard deviation	.119	.205	.360	.370	.198	.312	.287	.1781
Standard error	.049	.072	.127	.134	.070	.104	.102	.0701

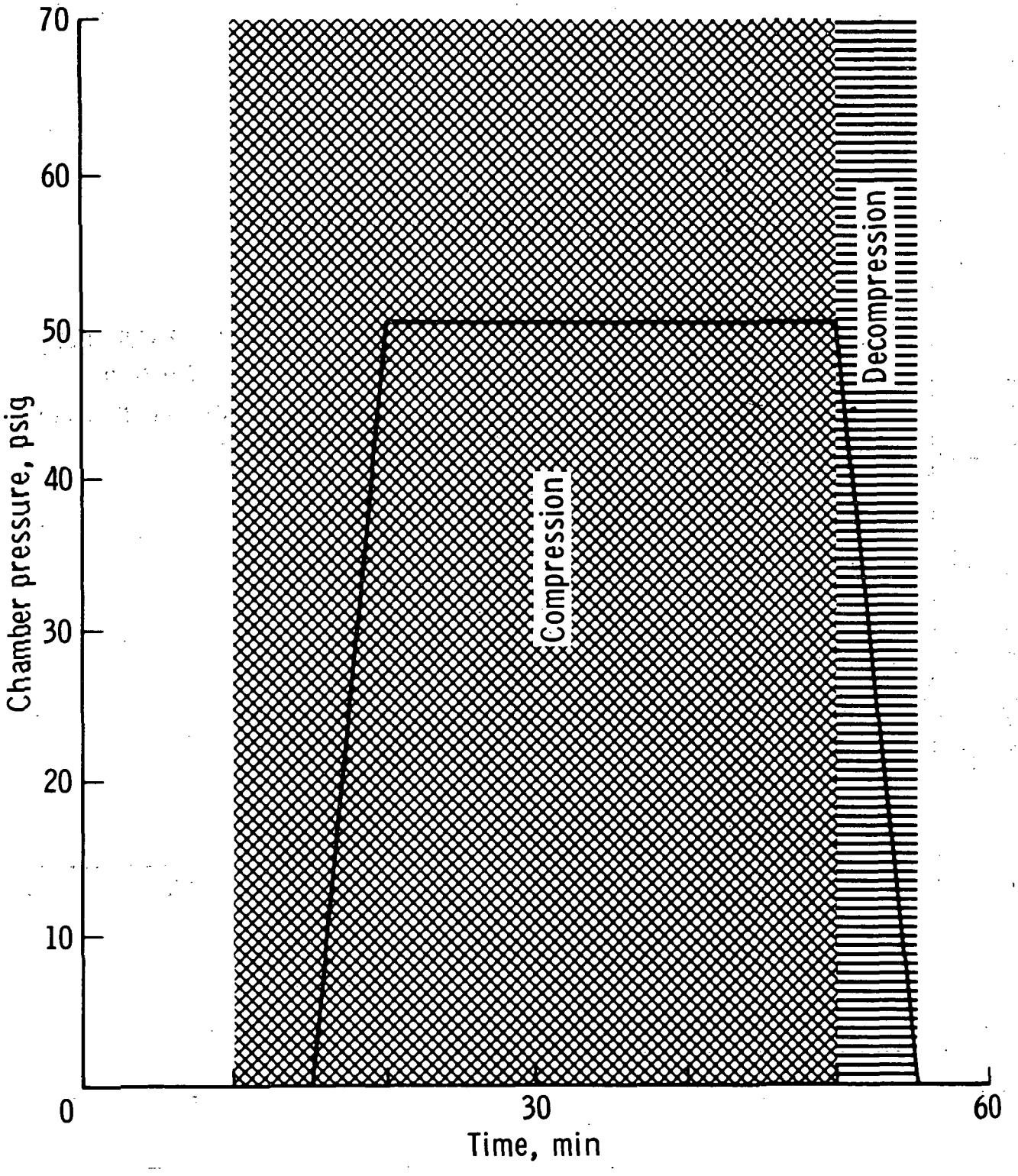

Figure 1. - Compression-decompression profile.

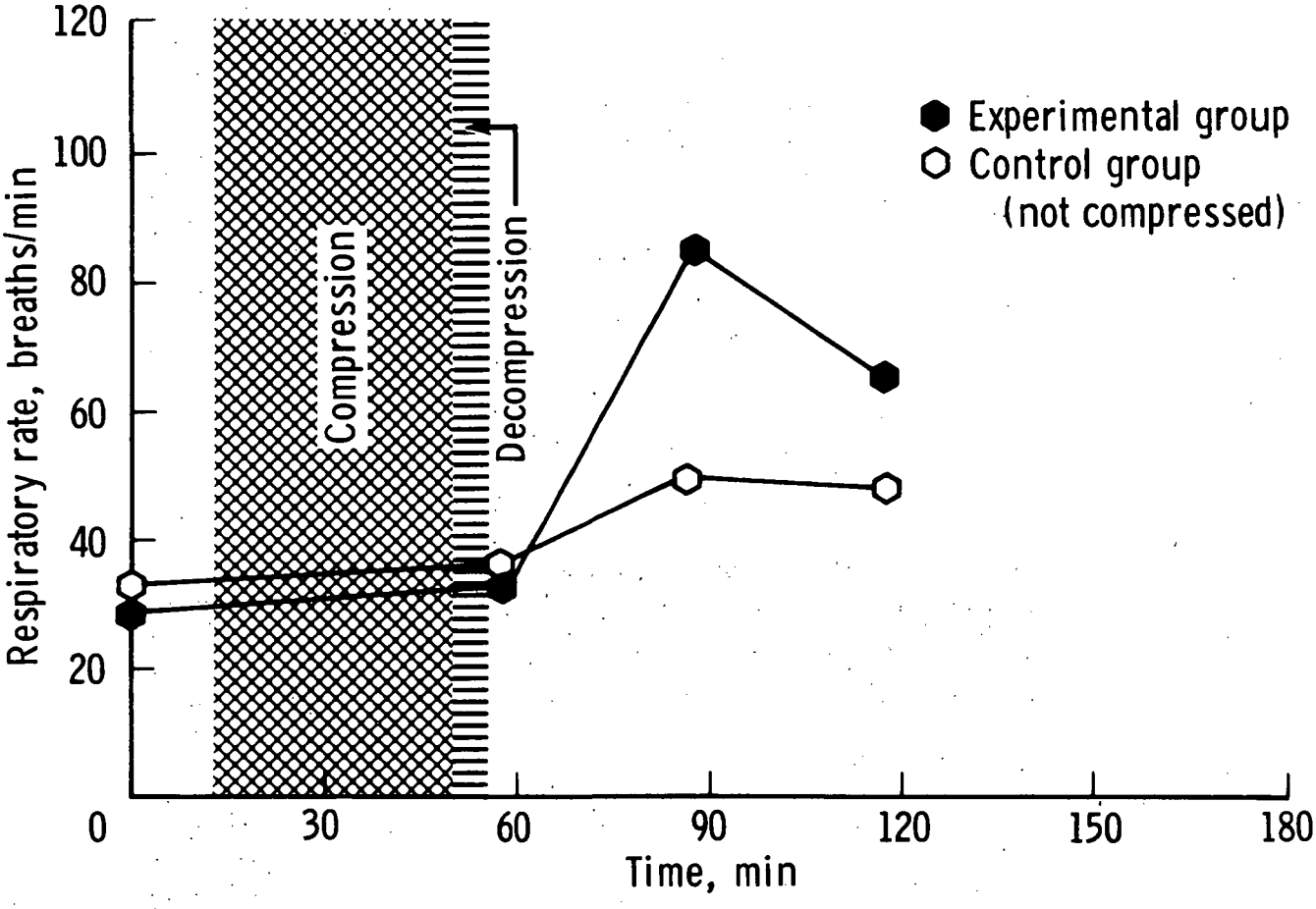

Figure 2. - Respiratory rate.

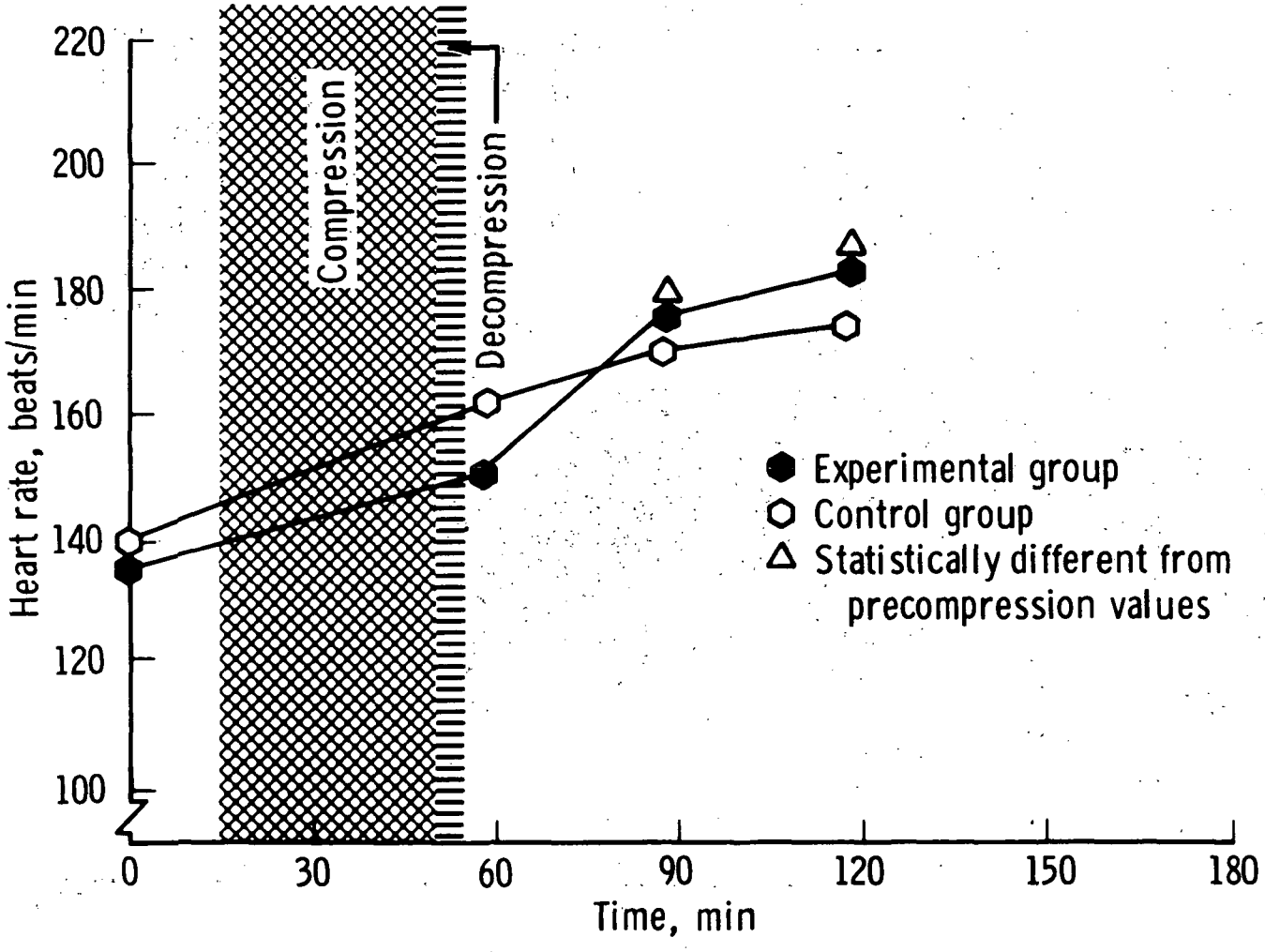

Figure 3.- Heart rate.

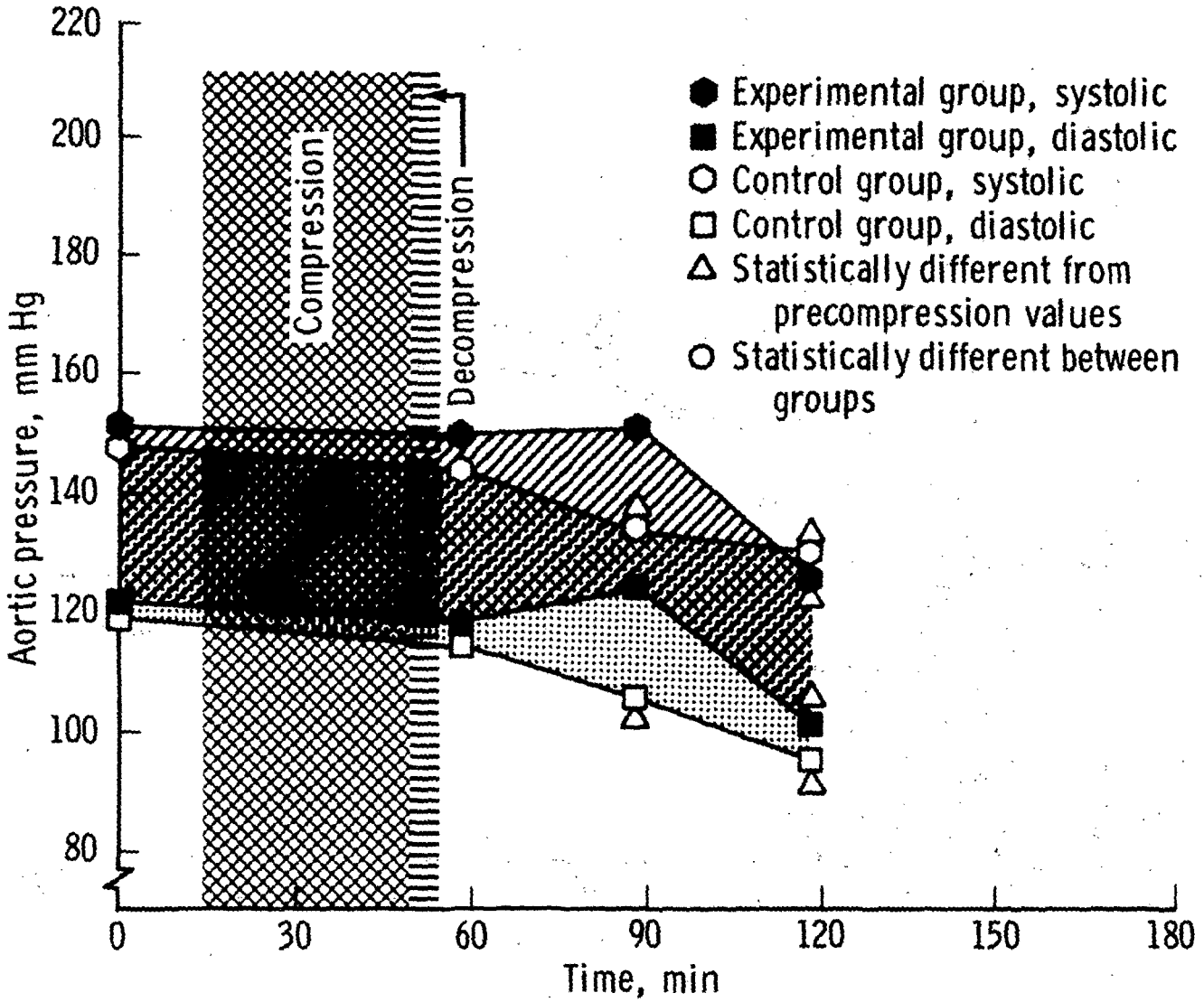

Figure 4. - Aortic pressure.

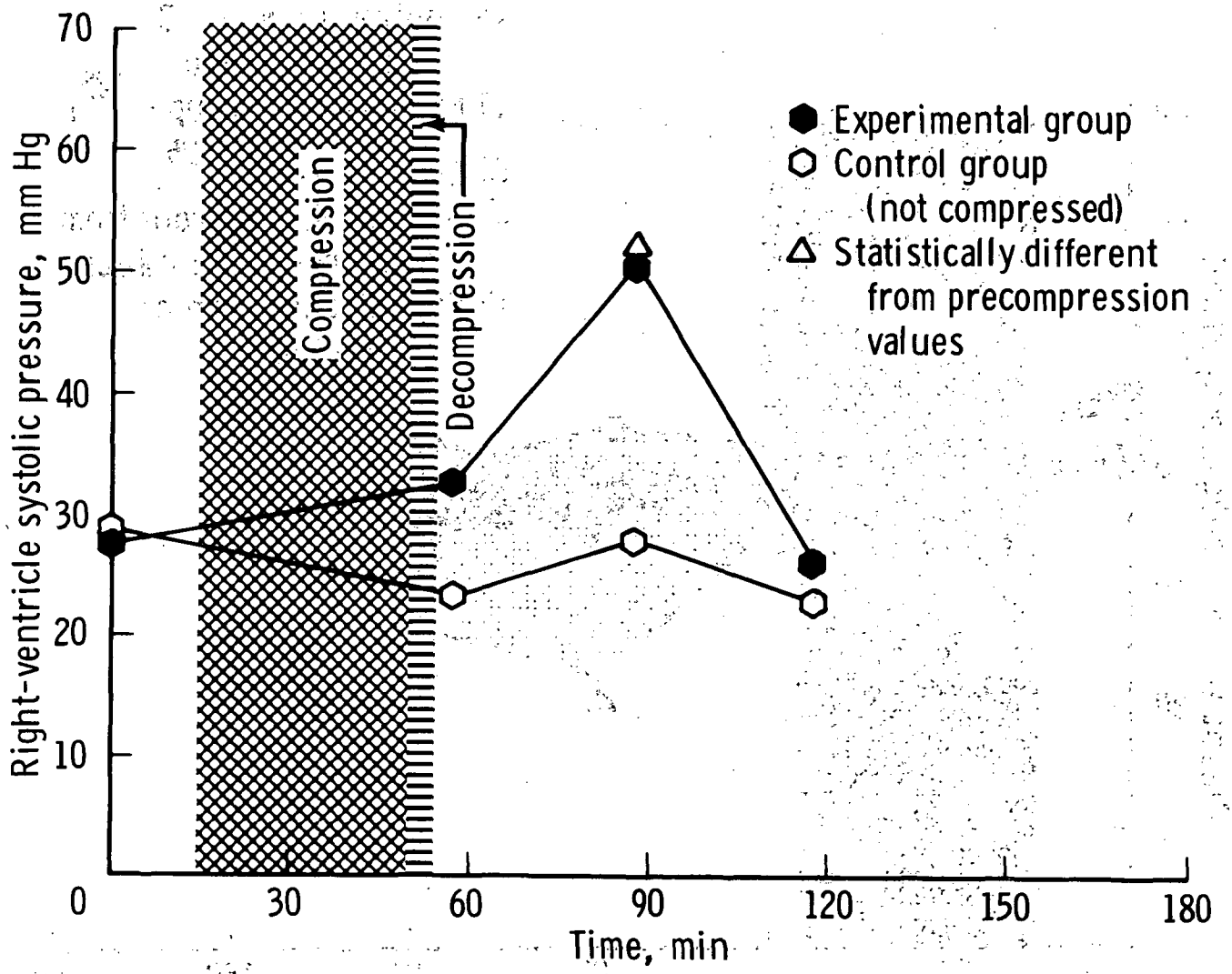

Figure 5. - Right-ventricle systolic pressure.

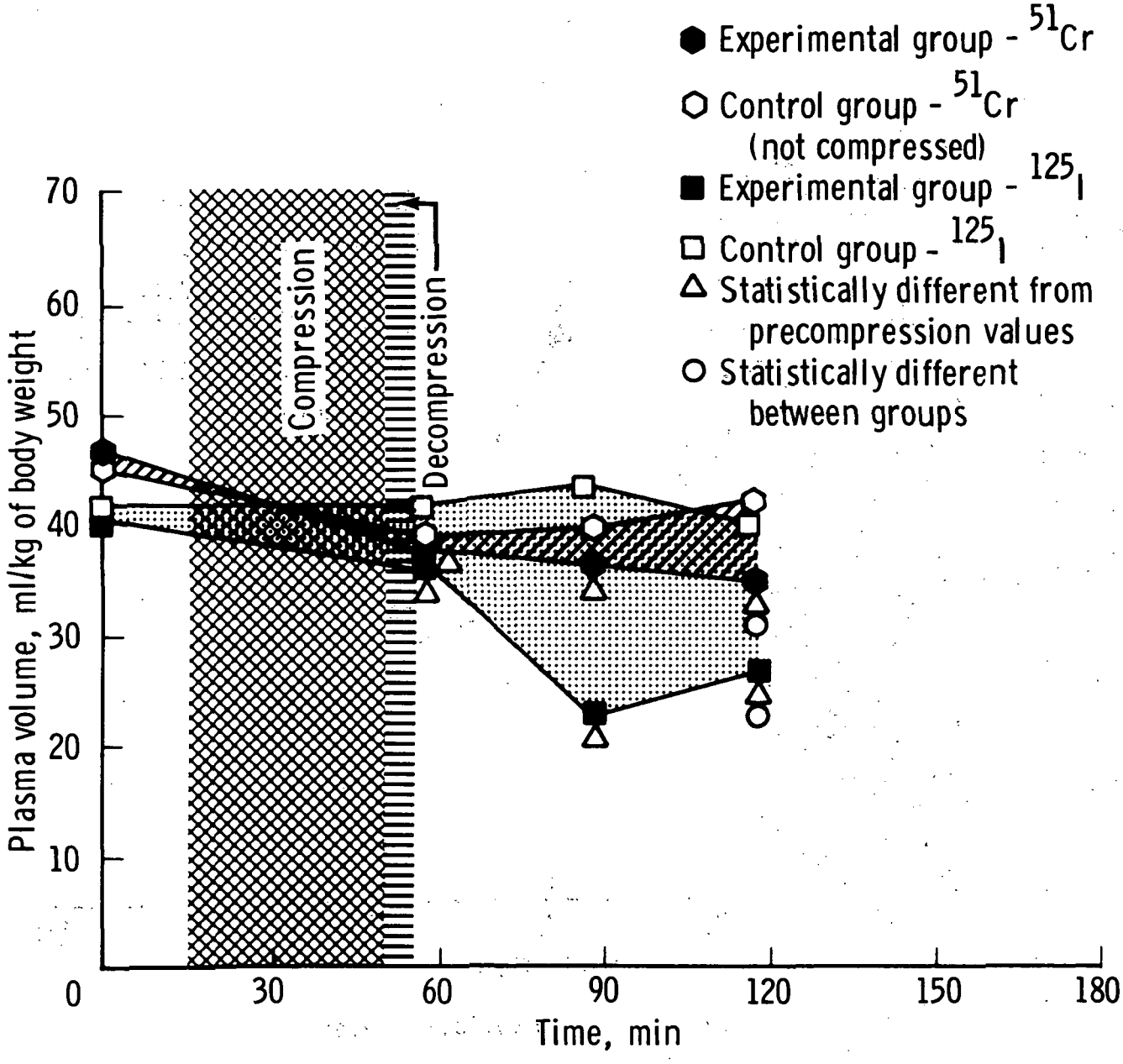

Figure 6.- Plasma volume per kilogram of body weight.

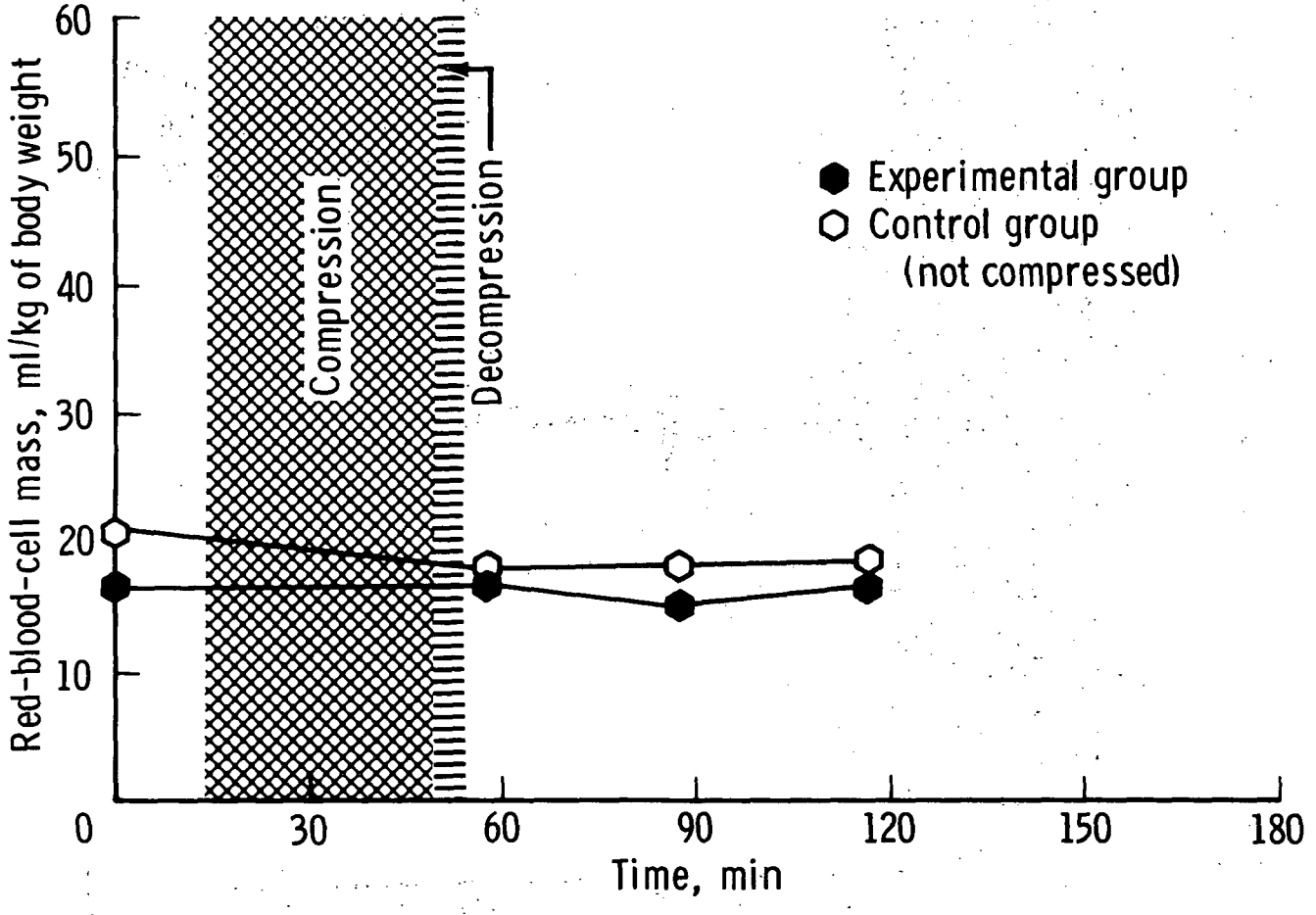

Figure 7. - Red-blood-cell mass per kilogram of body weight.

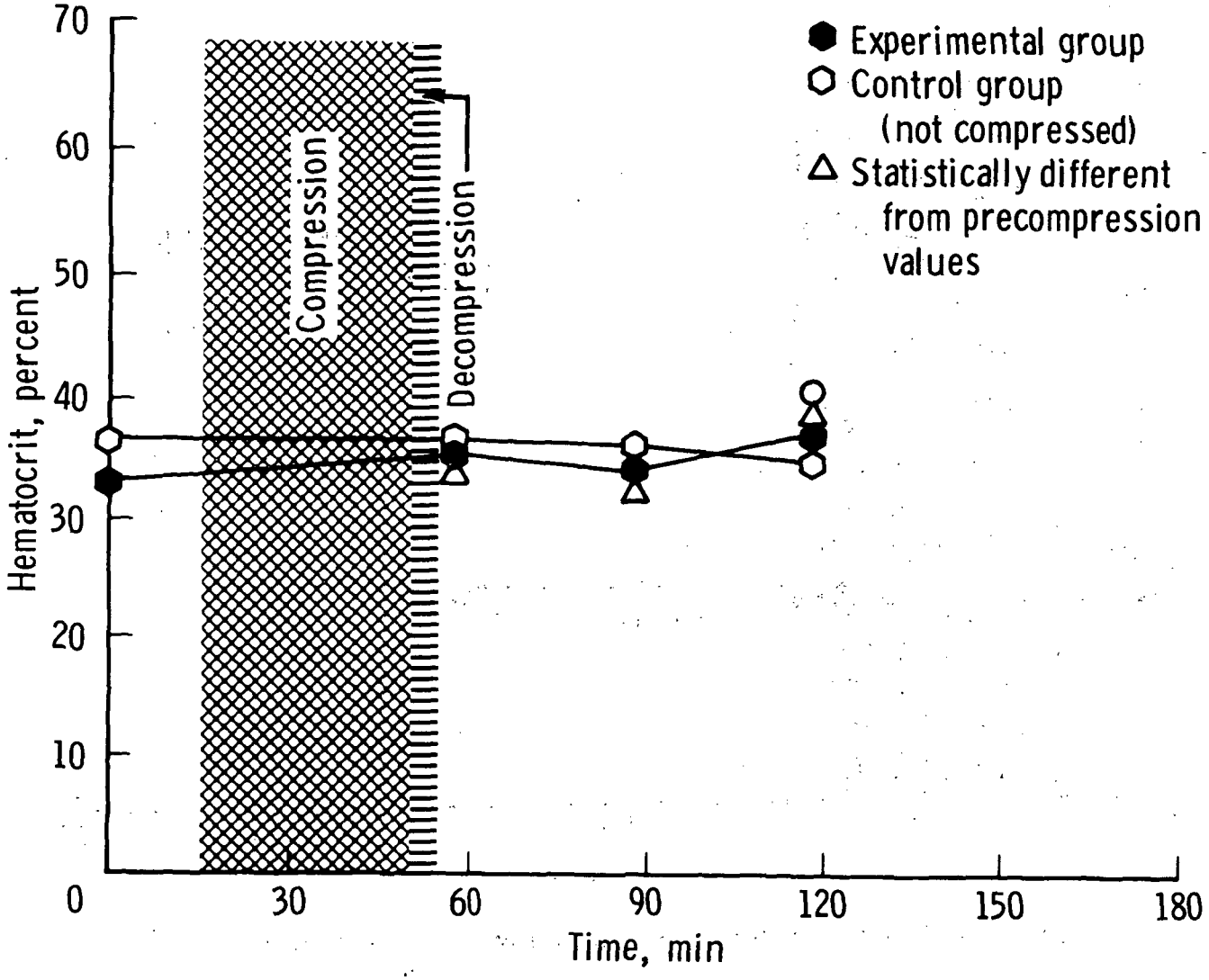

Figure 8.- Hematocrit.

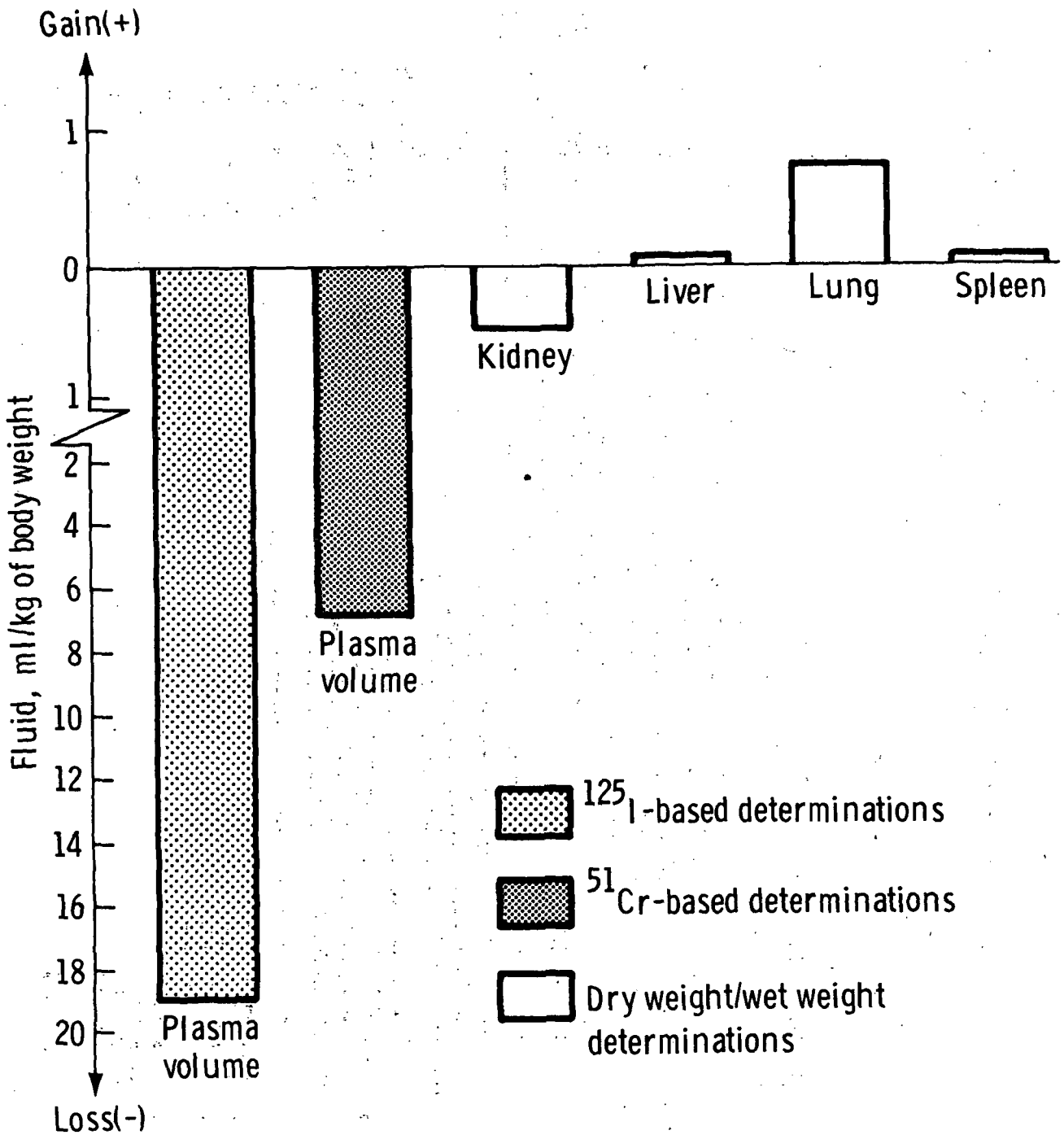

Figure 9.- Fluid shifts.

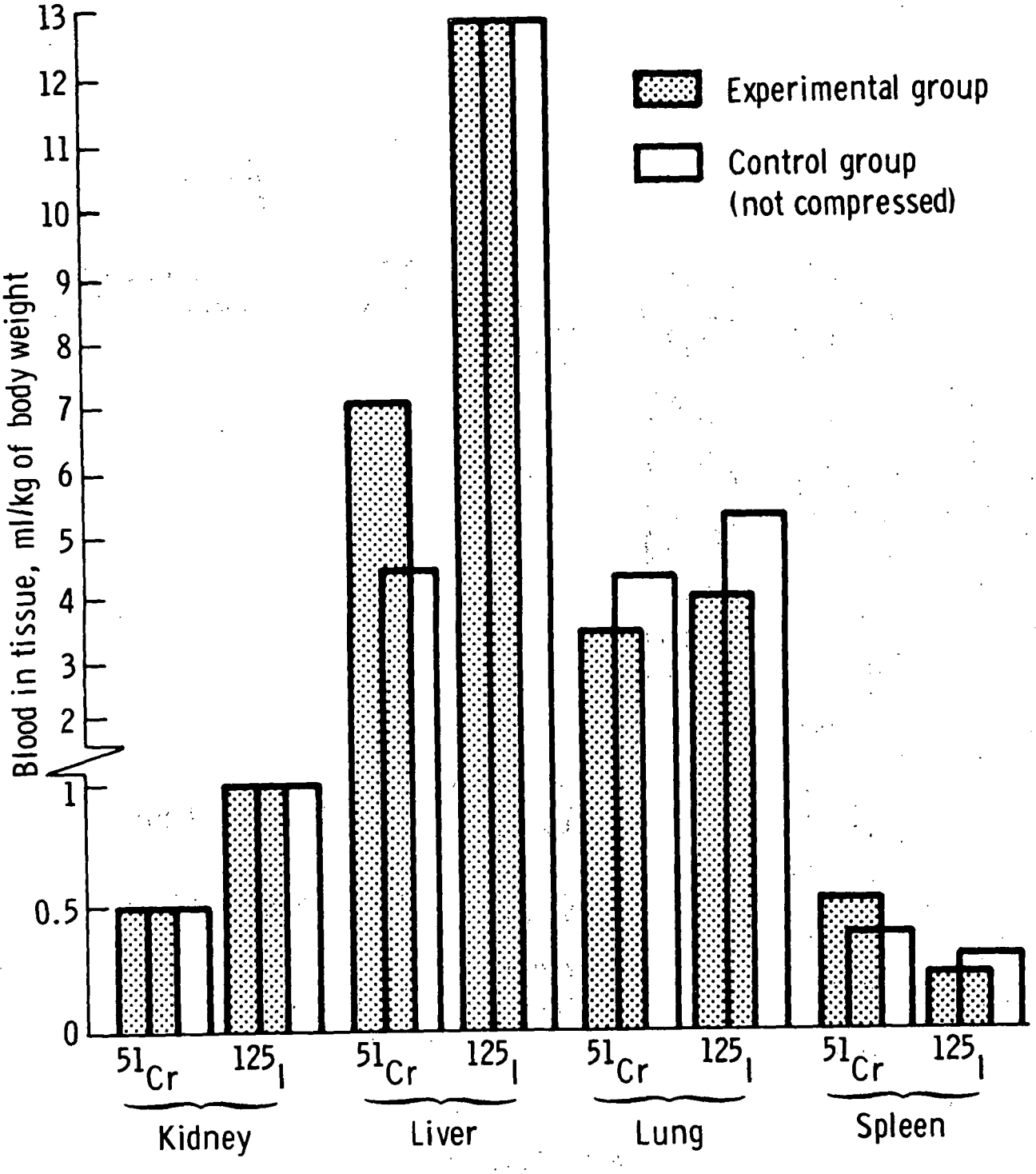

Figure 10.- Tissue-blood volumes.

VITA

James Allen Joki was born in [redacted], on [redacted], the son of Mr. and Mrs. Ole Enio Joki. After graduation from Ballard High School in 1960, he entered the University of Washington, Seattle, Washington. He completed his undergraduate work and received his Bachelor of Science in Aeronautical and Astronautical Engineering in 1965. For the next 5 years, he was employed as a flight controller at the National Aeronautics and Space Administration, Manned Spacecraft Center, Houston, Texas. In September 1970, he entered the graduate school at the University of Texas Medical Branch, Department of Physiology, at Galveston, Texas.

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