Experimental Hemorrhage: The Deleterious Effect of Hypothermia on Survival and a Comparative Evaluation of Plasma Volume Changes *

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INTRODUCTION

THIS STUDY was undertaken as part of a broad investigation of the physiologic effects of hypothermia which has been pursued in this laboratory for the past four years. It was stimulated by the gradually growing body of opinion that hypothermia might be valuable as a method of preventing or treating low blood volume shock. As the problem came into sharper focus, clarification of the response of the warm animal to hemorrhage became essential in order to establish a proper background for studying the effect of hypothermia.

Allen,[3, 4] we believe, was among the first to propose that shock might be favorably influenced by a lowered environmental temperature. Fay [22] was also in support of this opinion, although Cleghorn [14] found that dogs after hemorrhage survived better at average room temperatures than in either cool or hot environments. Blalock,[11] using tourniquet shock, and Antos,[5] in an experimental study using controlled hemorrhagic hypotension, both found that hypothermic animals could survive longer periods of hypotension but that the ultimate survival was not essentially improved. The results of other studies on various forms of shock [9, 20, 28, 43] at this time were also suggestive that a cold environment might be beneficial.

In 1952, Jaulmes,[34] and his French coworkers, re-introduced the concept with the development of the "lytic cocktail" and "artificial hibernation." Laborit,[35] on the basis of a few experiments using the Wiggers [51] technic of controlled hypotension to produce irreversible shock, vigorously championed the opinion that "artificial hibernation" was beneficial. He made no effort to distinguish between the effects of the multiple neurotoxins administered and those of hypothermia. However, it seemed that such animals, like those of Blalock and of Antos, could tolerate more prolonged periods of controlled hypotension. On the basis of this opinion, a clinical trial was attempted in Indochina, although apparently not until the soldiers had survived to reach a base hospital.[13, 37] Bobbio *et al.*[12] found that dogs would tolerate total exsanguination for 15 minutes before re-infusion if cold, while only three minutes if normothermic. This paralleled the well-known similar tolerance to circulatory arrest on the part of the hypothermic animal, and related little, if any, to the effect of cold on shock.

More recently, Overton *et al.*[38] have repeated the analysis of Laborit, but have carefully separated the effects of cold from those of chlorpromazine. Again, the experi-

* Presented before the American Surgical Association, White Sulphur Springs, West Virginia, April 13, 1956.

This work was performed as part of a research contract with the Office of The Surgeon General, United States Army (Contract No. DA-49-007-MD-572).

Aided in part by an institutional grant from the American Cancer Society.

ment was based on the Wiggers technic of controlled hemorrhagic hypotension. They found that hypothermia of about 30° C. prolonged the tolerable period of hypotension, chlorpromazine was even more effective, while the combination of both was best. However, the hemorrhage required to achieve equivalent hypotension was less in the cold animals than in the warm, particularly in the chlorpromazine groups. Fertitta and Scio [23] have reported improved survival of hypotension by the use of chlorpromazine. Friedman [27] also reported improved survival in precooled animals undergoing hemorrhagic hypotension, although most animals cooled after the bleeding failed to survive. Thus, many authors have left the suggestion that hypothermia and/or chlorpormazine might be beneficial in preventing death from hemorrhagic shock.

In considering an experimental plan for investigating the influence of hypothermia on tolerance for hemorrhage, we came to the conclusion that the standard methods in current use for producing irreversible hemorrhagic shock in the dog are unsuitable for a comparative study of the normothermic and hypothermic response to hemorrhage. In the method utilizing a period of controlled hypotension as elaborated by Wiggers, and modified by Fine,[25] the animal is subjected to a severe drop in blood pressure by massive bleeding. The hypotensive state thus established is maintained for the pre-determined time interval by the pressure level of a reservoir.

Our experience with hypothermic animals below 30° C. confirmed the observation of others. When animals are bled to a common arterial pressure, the volume of blood removed from the hypothermic animal is less than that removed from the normothermic animal. Thus, experiments performed with controlled hypotension compare only normothermic and hypothermic tolerance to hypotension; they do not compare tolerance to equal amounts of hemorrhage. Shock and hypotension cannot be considered synonymous, particularly in the hypothermic animal. Even in the warm animal, hypotension itself is known to be more tolerable with spinal anesthesia,[36] surgical sympathectomy,[26] and di-benamine.[42] Moreover, except for its capability of producing irreversible shock, the controlled hypotension experiment does not lend itself to a study of the body response to hemorrhage, since these very responses are nullified by the tight control of the blood pressure. The responses, in short, are themselves ablated. In addition, the situation is clinically entirely artificial; except for an occasional hypotensive anesthesia, *controlled hypotension* does not stimulate any clinical state seen following hemorrhage or trauma. For these reasons, we did not elect this technic.

The initial exsanguinating hemorrhage utilized in Walcott's [50] method for producing irreversible shock subjects the dog to a brief period of ischemic decerebration and total body hypoxia which are probably more easily tolerated by the cold than by the warm animal. The total bleeding volume in the warm animal, less the 25 per cent which was immediately returned, results in bleeding of massive proportions (45–50 ml./Kg.). Applying this method to hypothermic animals, it was again observed that the total available bleeding volume is greatly reduced in the cold state, because of the apparent sequestration of blood. The hypothermic animals were, as in the Wiggers technic, subjected to a less severe hemorrhage than were the warm animals. It was then decided that a uniform degree of hemorrhage might constitute a more realistic approach. Therefore, *a standard hemorrhage in per cent of blood volume* rather than some form of irreversible shock was elected as a method for the comparative study of the tolerance to hemorrhage of the normothermic and hypothermic dog.

In early experiments, normothermic and hypothermic (23°–26° C.) dogs were sub-

jected to acute hemorrhages ranging from 20 per cent to 40 per cent. These studies indicated that the tolerance of hypothermic dogs was considerably less than normothermic animals. Since it has been well documented that the dog's blood volume expressed as ml./Kg. varies considerably,[51] the uniformity of a hemorrhagic stress should be better achieved by removal of uniform fractions of actual blood volume. To investigate this observation, a specific hemorrhage in terms of blood volume was sought which was maximally severe but consistently sub-lethal in the normothermic animal. There are relatively few reports in the literature in which animals were bled a per cent of the measured blood volume rather than a fixed volume in ml./Kg. Walcott[50] bled unanesthetized dogs and found that 10 survived hemorrhages ranging from 44 per cent to 50 per cent, while 13 died following hemorrhages ranging from 45 per cent to 59 per cent. Fine[24] reported that unanesthetized dogs bled 40 per cent of their blood volume tolerated the hemorrhage with ease but that dogs anesthetized with pentobarbital died when subjected to 40 per cent hemorrhage. Further studies in this laboratory then indicated that a 35 per cent acute arterial hemorrhage in dogs anesthetized with pentobarbital was severe enough to produce a period of profound hypotension in most animals with survival of 100 per cent of untreated warm animals. This report concerns itself, therefore, with observations made in animals in which the volume of hemorrhage was uniform and in which response to this insult was not smothered by continued interference with compensatory mechanisms.

MATERIAL AND METHODS

I. *Design of Experiments.* Two primary objectives guided this work: (1) a comparative study of survival following equivalent hemorrhages in normothermic and hypothermic dogs; and (2) a study of dynamic fluid volume responses engendered by hemorrhage under normothermic and hypothermic conditions. Seventy-seven adult splenectomized mongrel dogs were used. Sixty-six animals were subjected to an acute arterial hemorrhage of 35 per cent of measured blood volume. Thirty-one experiments were performed at normal (Table I) body temperature and 35 were carried out at various stages of hypothermia ranging from 31° to 20° C. Eleven dogs, seven normothermic and four hypothermic, were not subjected to hemorrhage and provided control measurements. To study fluid responses, repeated measurements were made of blood presusre, hemoglobin concentration, hematocrit, plasma specific gravity and plasma volume. Cardiac rhythm was monitored by EKG throughout the experimental period.

TABLE I. *Summary Table of Experimental Animals*

	40° C.–35° C.	31° C.–28° C.	26° C.–20° C.
Group I	5		5
Group II	5	4	3
Group III	14	9	14
Group IV			
Controls	7	1	1
Ether	2		
Unanesthetized	2		
Morphine	3		2
Totals	38	14	25

All dogs reported for survival (Table I, Groups I, II and III) were anesthetized with intravenous sodium pentobarbital. Food was withheld but water allowed during the 12 hours prior to experiment. Dosage schedules were arranged with the objective of achieving in both normothermic and hypothermic animals the minimal anesthetic level capable of preventing shivering during sustained hypothermia. No premedication was administered. All animals had anesthesia continued for three hours following hemorrhage either by continued hypothermia or small doses of pentobarbital. After this period, the hypothermic animals were rewarmed. No supportive

therapy other than an endotracheal tube was given to any animal within the succeeding 12 hours. Animals surviving beyond this point were given intravenous fluids if too depressed to drink spontaneously and, in a few instances, penicillin was given for pulmonary infection. No plasma expanders were administered. Animals living for seven days after hemorrhage were classified as survivors.

The following protocols were employed:

Group I:

I.V. pentobarbital (28 mg./Kg.) → stabilization ½ hr. → { normothermic → hemorrhage; hypothermic → Cooled 1½ hrs. → hemorrhage }

Group II:

I.V. pentobarbital (28 mg./Kg.) → stabilization ½ hr. → Blood volume measurement 1 hr. → { normothermic → sustained anesthesia 1½ hrs. → hemorrhage; hypothermic → cooled 1½ hrs. → hemorrhage }

Group III:

I.V. pentobarbital (28 mg./Kg.) → stabilization 1½ hrs. → Blood volume measurement 1 hr. → stabilization ½ or 1½ hrs. → { normothermic → hemorrhage; hypothermic → cooled 1½ hrs. → hemorrhage }

In each of these dogs two plasma volume determinations were previously performed on different days. Blood volumes were calculated and the average value was used in determining actual hemorrhage volume.

Sustained anesthesia in the normothermic animals was accomplished by small frequent intravenous doses of pentobarbital (average: 6 mg./Kg./hour).

During the periods of stabilization and plasma volume measurements, anesthesia was maintained in both groups by small frequent intravenous doses of pentobarbital (average: 6 mg./Kg./hour).

No additional pentobarbital was ever required after cooling. It is to be noted that in Group III the total quantity of barbiturate administratered to normothermic and hypothermic animals was approximately equal whereas the duration of anesthesia prior to hemorrhage was prolonged in the hypothermic group because of the cooling. On the other hand, in Group II, hemorrhage was performed simultaneously in normothermic and hypothermic dogs, necessitating a greater total pentobarbital dosage in the normothermic animals.

Group IV included 11 animals, seven normothermic and four hypothermic, subjected to hemorrhage. These dogs provided control observations. In addition, two animals were anesthetized with ether, three with morphine plus sodium barbital and two trained dogs were studied in the unanesthetized state. These latter seven animals, all subjected to hemorrhage, provided data on the influence of various anesthetic agents. None of the animals in Group IV is included in the survival statistics since

all were utilized primarily for the investigation of dynamic fluid volume changes. No hypothermic animals anesthetized with morphine and barbital were included in survival studies since current investigations in this laboratory indicate that the use of morphine in animals cooled below 25° C. is associated with a high mortality rate due to cooling alone.[51]

In every dog subjected to hemorrhage, the actual volume of hemorrhage induced was calculated on the basis of the previously determined blood volume measured during the warm state. For reasons outlined above, a bleeding volume equal to 35 per cent of total blood volume was selected. In groups II and III bleeding volumes included all samples used in the measurements of plasma volume, hematocrit, hemoglobin concentration and plasma specific gravity so that the episode of acute major hemorrhage was somewhat less than 35 per cent, whereas the total was equal to 35 per cent of blood volume. All dogs therefore were bled an equivalent amount during the extent of the experiment.

All dogs had splenectomy one month or more prior to hemorrhage since it has been demonstrated [41] that blood volume determinations are more reliable in this species following splenectomy. It has also been demonstrated that the splenic response in dogs is of considerable magnitude and quite variable.[6, 7, 31, 49] Since such autotransfusion would interfere with the uniformity of the preparation and would alter some of the indices we wished to observe, there seemed no doubt that splenectomy was desirable.

II. *Plasma volume measurements and calculations.* Plasma volumes were determined by the dilution method using radioactive iodinated human serum albumin (RIHSA).* Albumin tagged with I^{131} was obtained from Abbott Laboratories. The ionic (free) radioiodine was less than 2 per cent as determined by dialysis and by precipitation. The labelled albumin solution was injected quantitatively through a large polyethylene catheter threaded into the abdominal aorta via the femoral artery. The syringe and catheter were thoroughly rinsed with blood following injection. Blood samples were obtained through the same catheter by first withdrawing 15 ml. of blood before collecting a 6 ml. analytic sample; the initial 15 ml. was then reinjected into the animal. Samples were placed in dry heparinized tubes. Plasma was then separated by centrifugation. All radioactivity measurements were made with a Berkeley well-counter (Model 2001) with decimal scaler. One milliliter samples of whole blood, plasma and standard solutions were counted. Radioactivity counts could be duplicated with an error of less than one per cent. A minimum of 10,000 counts was recorded for each specimen. The concentrations of radioactivity were determined in plasma and whole blood obtained at 20, 30, 40, 50 and 60 minutes after injection, and were then plotted against time on a semilogarithmic scale. Extrapolation provided counts per minute at zero time and plasma volume was calculated. When the plasma volume measurement was repeated later in the experiment, a sufficiently large dose of tagged albumin was injected to insure a concentration of radioactivity of an order of magnitude five to ten times greater than that of the residual concentration of RIHSA prior to reinjection.

Interpretation of changes in the distribution of intra- and extra-vascular fluid following acute hemorrhage in these studies is based on the alterations in concentration of plasma radioactivity. This method is essentially similar to that employed by Gibson [29] in 1937 using T-1824. Implicit in the acceptance of the procedure is approval of the following principles: (1) if acute hemorrhage occurred without compensatory alterations in intravascular fluid volume, the

* We wish to thank Dr. E. B. Reeve for many helpful suggestions concerning the technic of plasma volume determinations.

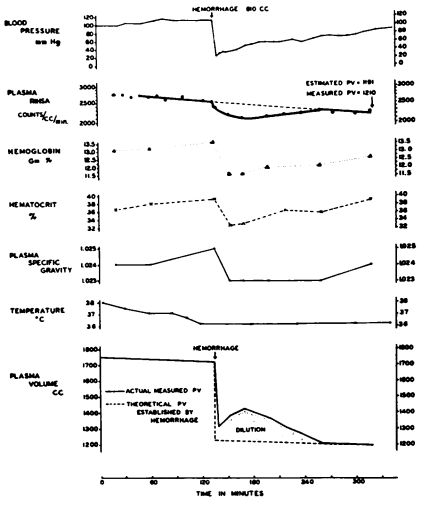

FIG. 1. Typical data obtained during an experiment involving 35 per cent hemorrhage in the warm dog. In this instance, the plasma volume is computed in cubic centimeters. Since the RIHSA slope suggests a constant blood volume prior to hemorrhage, the plasma volume at this time was assumed to be the same as the original measured plasma volume. Although this assumption is reasonably valid in the warm animal, it cannot be made in the cold animal (see text). Note that plasma volume changes as computed from RIHSA are supported by appropriate qualitative changes in plasma protein, hematocrit, and hemoglobin.

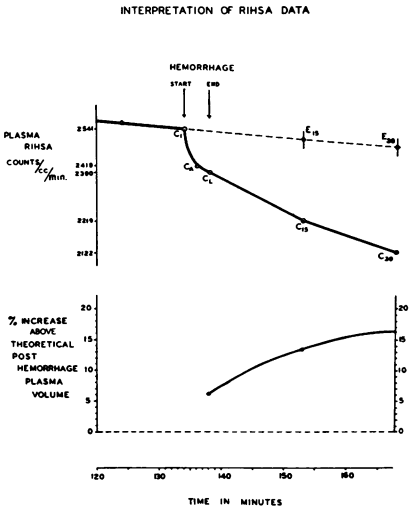

FIG. 2. Illustration of graphing technic used to calculate plasma volume changes in terms of the theoretical (undiluted) volume existing immediately post-hemorrhage (see text). The data here are the same as shown in Figure 1, but extended only from hemorrhage to 30 minutes later. We define the theoretical post-hemorrhage plasma volume as that volume of plasma which would remain in the vascular compartment following removal of blood if such a removal did not result in a change of RIHSA concentration in circulating plasma (dilution).

disappearance slope of plasma radioactivity would remain constant (this assumes no change in the biological decay rate of tagged albumin) and (2) if, on the other hand, hemorrhage is followed by a prompt decrease in the concentration of plasma radioactivity, the probable interpretation is that dilution of residual plasma radioactivity has occurred by the passage of extravascular fluid into the intravascular compartment. Other interpretations are also possible but confirmatory evidence of dilution had been obtained by simultaneous measurements of hematocrit, hemoglobin concentration, plasma specific gravity and repeat plasma volume measurements. Figure 1 is illustrative of an experiment in a normothermic dog. The overall similarity in the immediate post-hemorrhagic decline of all indices indicates that dilution actually occurred. Assuming, therefore, that the decrease in the concentration of RIHSA truly reflects this dilution, a quantitative interpretation of this fluid shift can be achieved. Figure 2 reproduces in detail the plasma radioactivity data of Figure 1 during the immediate post-hemorrhagic period. The disappearance curve (C_1, C_A, C_L, etc.) of labelled albumin represents measured changes in concentration of plasma radioactivity following hemorrhage. Also shown is the projected line (C_1, E_{15}, E_{30}) of decay which would be anticipated had hemorrhage not occurred or if, following hemorrhage, no dilution of plasma had occurred. The deviation from the projected line is considered to be the result of an increase in actual plasma volume over the theoretical plasma volume had no dilution occurred. *We define this theoretical post-hemorrhage plasma volume as that volume of plasma which would remain in the vascular compartment following removal of blood if this hemorrhage did not result*

in plasma dilution (no change in the disappearance rate of plasma RIHSA concentration).

The lower graph of Figure 2 shows the percentage increase of this theoretical post-hemorrhage plasma volume as calculated by the following method:

(a) The immediate divergence of the measured line C_1 to C_{30} from the projected line C_1 to E_{30} indicates that dilution begins before hemorrhage is complete.

(b) The total volume of plasma (already undergoing dilution) removed at hemorrhage is: $(100 - H)/100 \times S$, when H = the hematocrit of the total sample removed, and S = the volume of whole blood removed.

(c) The volume of *undiluted* plasma (total volume minus the dilution occurring during hemorrhage) included in the total sample at hemorrhage is: $C_A/C_1 \times$ the total volume of plasma removed (b) when C_A = the plasma concentration of RIHSA in an aliquot of the blood removed, and C_1 = the plasma concentration of RIHSA immediately before hemorrhage. (C_1 is used for convenience rather than a point E_A since by proximity the two are essentially equal.)

(d) The theoretical plasma volume (assuming no dilution) after hemorrhage is: (Plasma volume at time zero minus the plasma volume of analytic samples removed prior to acute hemorrhage) minus the volume of undiluted plasma removed at hemorrhage.

This hypothetical volume is represented by the broken line of the lower graph. Since it is evident that dilution occurred before hemorrhage was completed, the *actual* plasma volume (solid line of lower graph) remaining after hemorrhage exceeded the theoretical volume by a computable percentage.

(e) The percentage of theoretical plasma volume by which the actual plasma volume exceeds the theoretical volume at the end of hemorrhage is: $(C_1 - C_L)/C_L \times 100$, when C_L = the plasma concentration of RIHSA in the last 6 ml. of blood removed with hemorrhage. (C_1 is used for convenience rather than a point E_L since by proximity the two are essentially equal.)

(f) Similarly, at 15 minutes after hemorrhage the percentage of theoretical plasma volume by which actual plasma volume exceeds the theoretical volume is: $(E_{15} - C_{15})/C_{15} \times 100$, when E_{15} is the estimated concentration of RIHSA at 15 minutes following hemorrhage if no dilution of plasma has occurred.

Because of the stability of RIHSA disappearance in Figure 1, it is permissible to calculate post-hemorrhagic fluid shifts in this particular experiment in absolute terms (bottom line, Fig. 1).* However, in many instances the rate of disappearance of RIHSA prior to hemorrhage is less stable due to alterations occurring in plasma volume and the calculation of actual volumes is less secure. Nevertheless, the relationship between theoretical post-hemorrhage plasma volume and the actual volume in percentage deviations from this volume can still be defined on the basis of the following formula.

* Plasma volume at time zero = 1751 ml. Analytic samples withdrawn before hemorrhage = 34 ml. Plasma volume at the time of hemorrhage = 1,717 ml. Hematocrit of hemorrhage sample = 36 per cent. Diluted plasms removed at hemorrhage = 518 ml. Undiluted plasma removed at hemorrhage = 493 ml. Theoretical plasma volume at end of hemorrhage = 1,224 ml. Per cent increase above theroetical plasma volume at end of hemorrhage = 6.3 per cent. Actual plasma volume at end of hemorrhage = 1,301 ml. Per cent increase above theroetical plasma volume 15 min. after hemorrhage = 12.3 per cent. Actual plasma volume 15 minutes after hemorrhage = 1,374 ml. As shown in Figure 1, plasma volume was further decreased after hemorrhage by the withdrawal of additional samples (33 ml.) during the fourth, fifth and sixth hours. A repeat plasma volume measured three hours after hemorrhage was 1,210 ml. Using the procedures outlined, the predicted plasma volume, based on the concentration of labeled albumin, was 1,191 ml. Thus, the difference between predicted and measured volumes was 19 ml.

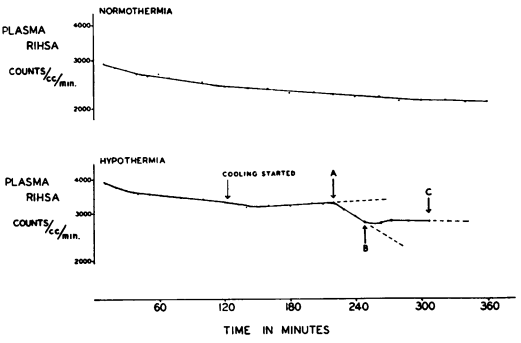

FIG. 3. Six-hour control RIHSA curves, one in the normothermic and one in the hypothermic (20° C.) dog, are presented. At normal temperature, the rate of disappearance of RIHSA is a stable slope, whereas in the cold dog blood volume changes are occurring constantly causing an unstable RIHSA disappearance slope. Therefore, projection of any portion of the line in the cold animal cannot be used reliably, as illustrated by the difference in these projections had the dog been bled at point A, B, or C. For this reason, a mean biological decay slope parallel to that illustrated for this warm dog is used for computations in both warm and cold animals (see text).

The percentage of theoretical volume by which actual volume exceeds theoretical volume at any time (x) is: $(E_x - C_x)/C_x \times 100$, when E_x = the concentration of RIHSA if no dilution occurred at any time (x) after hemorrhage and C_x = the concentration of RIHSA as actually measured at any time (x).

The obvious problem in dealing with unstable disappearance slopes is the slope of the projected line of concentration (C_1, E_x). For example, Figure 3 depicts a highly unstable line of measured RIHSA concentrations. If, at various locations on this line (e.g.: A, B, C) hemorrhage had been induced, what slope should one use for the projected line of RIHSA concentrations which would be anticipated if no dilution occurred?

In order to clarify this problem, the RIHSA disappearance slope of seven dogs was determined during the 120 to 300 minute period after RIHSA injection during which the plasma volumes appeared to be stable. The mean disappearance slope during this stable period exhibited a half-time of 810 minutes (fractional disappearance rate: 0.000856 per minute). Maximum measured deviations from this mean slope at three hours were within ± 3 per cent. Further, to test the validity of this slope, plasma volumes estimated by deviations from this mean slope were compared to *actually measured* plasma volumes approximately five hours after the first RIHSA injection. In 14 animals, ten of which had been subjected to 35 per cent hemorrhage, the average difference between *estimated* and *measured* plasma volumes was 4 per cent and in no instance exceeded 10 per cent. Since the studies reported in this paper relating to early plasma volume changes following hemorrhage make use of this mean slope for only 30 minutes, the possible error is considered to be insignificant. Moreover, since we assume that any variations in the disappearance slope of RIHSA are in fact due to plasma volume changes and not to any fundamental alteration in the biological decay rate, use of a stable RIHSA disappearance slope seemed the most desirable projection. Therefore, in all computations of plasma volume changes in either warm or cold animals following hemorrhage, this mean slope was used.

III. *Methods.* Hemorrhage was accomplished by rapid bleeding from the aorta through a polyethylene catheter sufficiently large to permit withdrawal of 200 ml. per minute. The time required varied between three and six minutes.

Hypothermia was achieved by surface cooling in an ice water bath as previously described in reports from this laboratory.[47, 48] All hypothermic animals had respiratory support. In addition, both normothermic and hypothermic animals in group III had respirations supported with pure oxygen using a respirator with a CO_2 absorber. Respiratory rate was adjusted to maintain arterial blood pH between 7.35 and 7.45 as determined on a pH meter (Beckman, Model G).

TABLE II. *Mortality Rate of Hemorrhaged Anesthetized Dogs at Different Temperatures*

Temperature Range	Number	Survived	Died	Mortality
40–35°	24	24	0	0
31–28°	13	12	1	8%
26–20°	22	4	18	82%

Blood pressures were recorded by a mercury manometer connected to the aortic catheter. Mean pressures were calculated as diastolic pressure plus ⅓ pulse pressure.

Rectal temperatures were recorded with mercury thermometers.

Hematocrits were determined by the method of Hlad and Holmes.[33] Hemoglobin concentration was measured by the Wintrobe technic,[53] and read on a Klett-Summerson photo-electric colorimeter. Plasma specific gravity was determined by the falling drop procedure.[39]

Blood volume was determined by computation using RIHSA plasma volume and hematocrit.

RESULTS

I. *Survival.* The variations in the protocol of Groups I, II and III had no discernible effect on survival. Therefore, the three groups are summarized together in Table II. No deaths occurred in normothermic animals. In contrast, there was an 82 per cent mortality in the 26° – 20° C. group. This clearly emphasizes that a 35 per cent hemorrhage is well tolerated in the normothermic animal and is highly lethal in lower ranges of hypothermia. In the intermediate range, 31° – 21° C., one dog of 13 died, a mortality of approximately 8 per cent.

Of the nineteen animals which died, 15 expired during the three-hour period of hypothermia following hemorrhage, usually in ventricular fibrillation as demonstrated by electrocardiography. The four remaining deaths occurred within 12 hours of rewarming with the classical manifestations of irreversible shock.

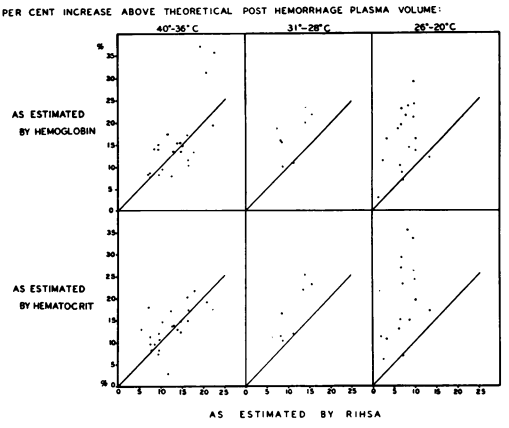

FIG. 4. The plasma volume changes as computed by RISHA are compared to those computed by hemoglobin and hematocrit at various temperature levels. The line drawn in all graphs was derived from the data in the normothermic group. Although there is positive correlation at all temperatures, the red cells are more diluted than the tagged albumin in the colder temperature ranges.

II. *Dynamic fluid responses.* To confirm the interpretations of the RIHSA data in terms of redistribution after hemorrhage, the concomitant changes in hematocrit, hemoglobin concentration and plasma specific gravity were analyzed. The relationship between plasma volume changes as measured by RIHSA and the red cell indices is shown in Figure 4. There is a positive correlation at all temperature levels. However, with progressive hypothermia there is progressive deviation of the estimates using the red cell indices above the slope found in normothermic animals, indicating that the dilution of red cells is greater than that of tagged albumin following hemorrhage during hypothermia. Ignoring certain implications to be discussed later, it is evident that the effect of hypothermia on these indices of dilution is qualitatively similar although quantitatively different. The directional changes in specific gravity and plasma RIHSA concentrations were consistent in both the warm and hypothermic experiments. However, quantiative correlation between these two measurements was less consistent than that

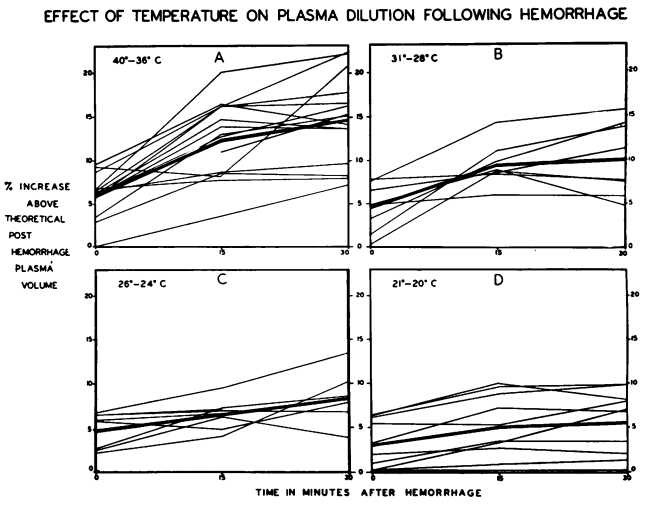

FIG. 5. A number of plasma volume changes following hemorrhage are plotted for each temperature range, and the means are shown in the dark lines. Note that with each decrement in temperature, the amount of dilution of the plasma is decreased.

between RIHSA and the red blood cell indices.

All subsequent interpretations in this paper are derived from RIHSA data.

Plasma Dilution. From observations during the three hour period following acute arterial hemorrhage the statement may be made that maximum plasma dilution was usually established within 30 minutes in both normothermic and hypothermic experiments. Moreover, as was illustrated in Figure 1, and will be seen again in Figure 10, dilution usually began to decrease after 30 minutes in the warm animals. This was also the pattern in the hypothermic animals. The time required for maximal dilution appeared to be approximately equal in both hypothermic and normothermic animals (Fig. 5). However, the volume of the dilution was greatly reduced in the colder temperature groups.

Plasma Dilution and Body Temperature. The relationship between hypothermia and plasma dilution is further illustrated in Figure 6. Although individual variation within each temperature level was considerable, analysis showed that mean differences in plasma dilution between all hypothermia groups and the normothermic groups are significant. There is a striking progressive decrease in the degree of plasma dilution with each decrement in the temperature at which hemorrhage occurred.

Plasma Dilution and Blood Pressure. Figure 7 illustrates the blood pressure response following hemorrhage in each of four temperature groups. After the initial fall in blood pressure the normothermic animal responded with a rapid rise in pressure, so that 30 minutes after hemorrhage, seven of eight normothermic animals had attained a mean pressure of 80 mm. Hg or higher, and after 60 minutes a pressure of 100 mm. Hg or above. In contrast, in the 21°–20° C. group the mean pressure of only one animal ever exceeded 35 mm. Hg in the 180-minute period following hemorrhage. The 31°–28° C. and the 26°–24° C. groups showed intermediate gradations of response. Three pertinent conclusions can be made from these data. First, the mean pre-hemorrhage blood pressure declines as body temperature is lowered; second, the maximum fall in blood pressure decreases as body temperature falls; and third, progressive decrease in temperature is accompanied by progressively prolonged hypotension.

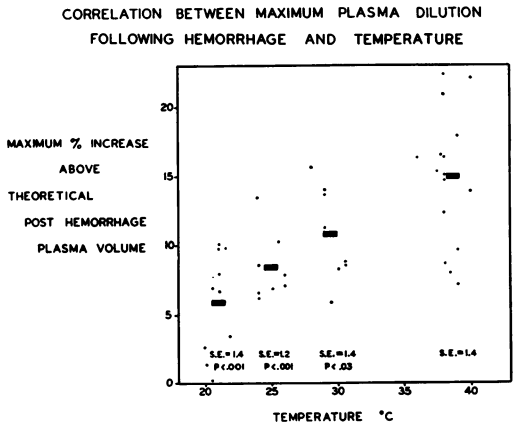

FIG. 6. The maximum change in plasma volume within 30 minutes following hemorrhage is charted for the various temperature groups. The means and standard errors of the means of each group are shown, together with "p" values comparing each hypothermic group to normothermia. The differences in the means between the normothermic and the hypothermic groups are significant.

Since decreasing body temperature altered the response to hemorrhage of both plasma dilution and blood pressure, it appeared logical to explore the relationship between these two variables. When maximum percentage increase in the theoretical plasma volume was plotted against maximum blood pressure decrease induced by hemorrhage (Fig. 8), a definite correlation became apparent. The four temperature groups were plotted separately in Figure 9. Although the correlation between plasma dilution and blood pressure decrease was extremely good in the normothermic and in the 21°–20° C. groups (A and D), it was less impressive in the intermediate temperature groups (B and C). Nonetheless, the overall correlation between plasma dilution and blood pressure fall indicated that hypothermia may exert its effect on plasma dilution after hemorrhage by virtue of its effects on blood pressure.

Confirmatory evidence for this view is obtained from studies on normothermic dogs of Group IV which were subjected to hemorrhage. Two of these animals were unanesthetized, two were under ether and three were anesthetized with morphine plus barbital. Table III compares the blood pressure immediately prior to hemorrhage, the blood pressure decrease after hemorrhage and the maximum percentage increase above theoretical post-hemorrhage plasma volume in dogs anesthetized with pentobarbital with those under different anesthetic conditions (Group IV). The mean percentage plasma dilution in Group IV was considerably less than in Group III. However, the blood pressure fall was also less. Therefore, the previously described relationship between plasma volume changes and blood pressure fall was again demonstrated; but, in this case, the two groups of animals were at the same temperature.

TABLE III. *The Effect of Anesthetic Agent on Blood Pressure and Plasma Volume Changes in Normothermic Animals*

	(Group III) Pento-Barbital (15 Animals)	(Group IV) Unanesthetized, Morphine and Barbital Ether (7 Animals)
Mean pre-hemorrhage blood pressure (mm. Hg)	135	96
Mean blood pressure fall (mm. Hg)	85	46
Mean plasma dilution (%)	15	9

Fate of Plasma Volume Increase. Normothermic experiments in which the plasma volume changes were followed beyond 30 minutes showed a rather consistent reversal of the initial dilution following hemorrhage. This escape of dilution fluid back into the extra-vascular compartments appeared to accompany the recovery of blood pressure as illustrated by the four examples in Figure 10. The amount of the early dilution fluid which was subsequently lost from the vascular compartment varied considerably, as did the time necessary for the reversal to take place. However, at least some loss of dilution uniformly occurred during the second and third hours after hemorrhage.

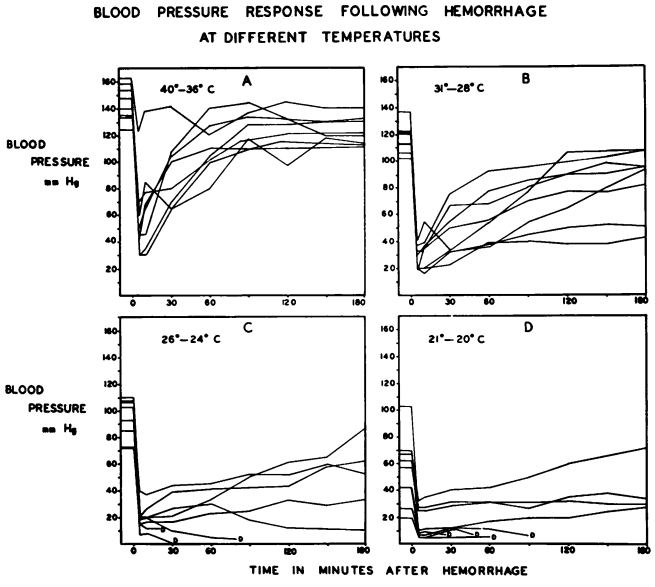

FIG. 7. Several mean blood pressure responses following hemorrhage are shown at each temperature level. The magnitude of the fall in blood pressure following hemorrhage is progressively smaller with cooling. The warm dogs spontaneously recover their blood pressure usually within an hour. In colder groups, the blood pressure, initially depressed by hypothermia and subsequently further depressed by bleeding, shows progressively less tendency to rise toward pre-hemorrhage levels as long as the dog remains cold.

The rise and maintenance of the blood pressure occurred at a time when plasma volume was decreasing.

Insufficient studies in hypothermia animals were made to analyze the late course of dilution under these conditions.

DISCUSSION

These studies clearly demonstrate that lower ranges of hypothermia greatly decrease the tolerance of splenectomized dogs to acute hemorrhage. Paradoxically, they confirm the findings of other investigators that hypothermia improves tolerance to hemorrhagic *hypotension*. Some dogs survived periods of hypotension (up to three hours at less than 35 mm. Hg) which almost invariably have been fatal in normothermic animals. However, observations like the latter—heretofore the sole foundation for opinion concerning the effect of hypothermia on tolerance to hemorrhage—have only partially resolved the problem, for the fact remains that mortality rate in colder dogs subjected to hemorrhage was remarkably high.

Clearly, the cause of death in the hypothermic animals is critical to this analysis. Of the 15 animals which died during the hypothermic period ventricular fibrillation was known to be the final event in 13. In this laboratory, this degree of hypothermia alone rarely has been observed to kill the animal. Thus, hemorrhage appears to have been a fibrillatory stimulus. It is to be noted, however, that in these studies the speed with which blood was removed was greater than that reported by most workers. And, in addition, the degree of hypothermia (26–20° C.) imposed was more intense. Since fibrillation was such a frequent cause of death it might well be possible to reduce this mortality rate if fibrillation were effectively prevented.

Hypothermia does not always obfuscate the mechanisms producing irreversible shock following hemorrhagic hypotension. In four animals death occurred in the 12

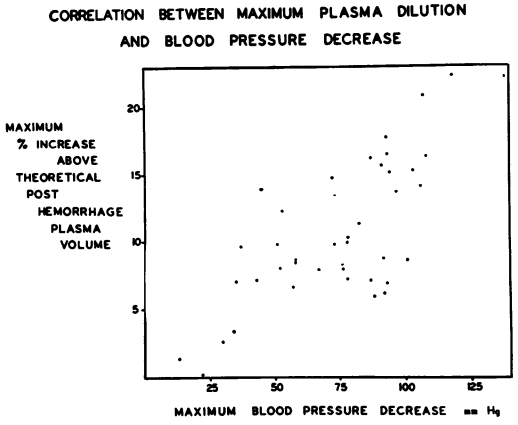

FIG. 8. The maximum change in plasma volume within 30 minutes following hemorrhage is plotted against the maximum decrease in mean blood pressure. The data suggest that the magnitude of plasma volume shift following hemorrhage may be related to the magnitude of drop in blood pressure, irrespective of temperature.

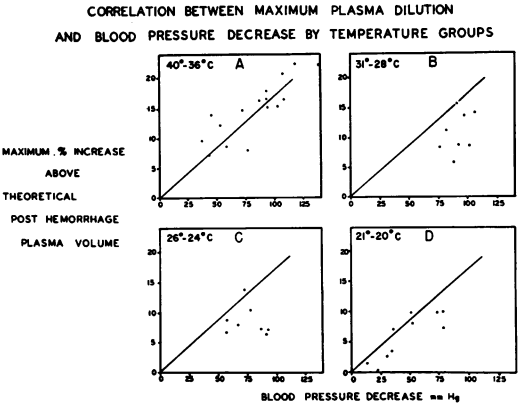

FIG. 9. The relationship between plasma volume increase and blood pressure fall is shown for each temperature level. The slope illustrated in each graph was derived from the data in A. The correllations at normal temperature and at 21–20° C. are extremely good.

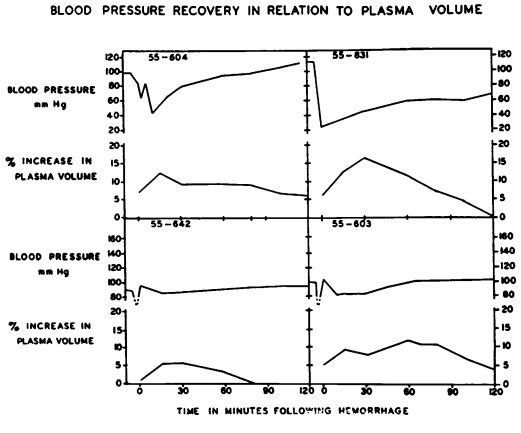

FIG. 10. Data are presented from four animals in which the mean blood pressure returned toward pre-hemorrhage levels, yet during the same period of time the increase in plasma volume was disappearing. The chart suggests that plasma dilution is not essential to the maintenance of blood pressure recovery following hemorrhage.

hour period following rewarming and was associated with the pathologic changes commonly seen in lethal shock. Friedman [27] also noted that hypothermia often postponed but did not prevent delayed death following rewarming after hypothermic hypotension.

One of the suggested alterations in hypothermic animals which may be related to survival following hemorrhage is a decrease in what has been termed the effective blood volume. Bigelow *et al.*[10] had early described, on the basis of direct visualization of capillaries, intravascular agglutination of erythrocytes. D'Amato and Hegnauer [19] reported a reduction in circulating blood volume during hypothermia which they suspected was on the basis of "trapping" of blood. Crosbie *et al.*[18] also obtained evidence for sequestration and indicated that the spleen, liver and intestine were mainly responsible. Our data in Fig. 4 are compatible with this point of view and suggest that as hypothermia became more intense less red cells than plasma protein became available for dilution.

Our studies reaffirm the direct relationship between blood pressure and plasma volume following hemorrhage.. This is an old and well-documented concept. Sherrington [45] in 1893 acknowledged the "numerous observations" of Ludwig and his pupils on this relationship. Cohnstein [15] furthered the concept by clarifying the effect of blood pressure in facilitating diffusion of fluids across capillary walls. Starling,[46] in his classic contribution, clearly defined the fundamental interrelationships of plasma volume with hydrostatic and on-

cotic pressures. Scott [44] illustrated the persistence of the correlation between blood pressure and blood volume during a wide variety of procedures producing significant alterations in pressure. Both Hirota [32] and Adolph [1, 2] subsequently demonstrated that the dilution of plasma following hemorrhage was very rapid, that the fluid subsequently escaped from the vascular compartment, and that both phenomena appeared to be the result of alterations in blood pressure. Gibson [30] and Price [40] have ascribed blood volume changes during surgical procedures to deviations in blood pressure.

Although admittedly improbable, the possibility remained that this basic biophysical relationship might be altered by hypothermia. The data shown in groups B and C in Figure 9 suggest that perhaps it was, at least quantitatively, since in these hypothermic animals plasma dilution after hemorrhage was somewhat less in relation to blood pressure fall than in the normothermic group. However, it is possible that, at specific levels of hypothermia, changes in vasomotor activity may so alter the relationship between arterial pressure and capillary pressure that the correlation between arterial pressure and plasma volume is less direct. Nevertheless, the qualitative relation between blood pressure and plasma volume still appears to exist and, indeed, the correlation exhibited in the range 26–20° C. (group D) was excellent. Therefore, while it is apparent that hypothermic animals exhibited less plasma dilution after hemorrhage than the normothermic group (Figs. 5 and 6) it is also evident that the magnitude of blood pressure fall was similarly decreased during hypothermia and that the smaller degree of plasma dilution found in the hypothermic groups appeared to be mainly attributable to this decreased blood pressure fall.

Although these studies were mainly concerned with the course of events occurring immediately after hemorrhage it may be pointed out that in all normothermic animals plasma dilution diminished as the blood pressure rose. It is of interest that a recent study [8] describes a similar course of events following acute blood withdrawal in unanesthetized humans. Furthermore, in the experiments reported here, plasma dilution persisted in animals which failed to show a sustained rise in pressure. This directly suggests that following hemorrhage changes in blood volume are influenced by blood pressure rather than blood pressure being maintained by a plasma volume increase. The possible importance of this relationship between arterial pressure and plasma dilution following hemorrhage should be recognized for herein may lie the explanation of the findings in a patient who is admitted to the surgical ward with a well-maintained blood pressure, normal hematocrit, and normal hemoglobin but with a dangerously low blood volume. Unfortunately, observations in these studies on the course of plasma volume changes in hypothermic animals beyond the immediate post-hemorrhagic period are too few in number to permit discussion.

It is evident that anesthetic agents may influence the physiological response to hemorrhage. For example, it has been suggested by Elman *et al.*[21] and by Courtice [17] that barbiturates may block or reverse post-hemorrhagic plasma dilution. Unfortunately, blood pressure changes were not described by these workers. Our data (Table III), in contrast, showed that the immediate plasma dilution following hemorrhage which occurred during pentobarbital anesthesia was actually greater than that exhibited by dogs which did not receive this agent. It is of interest that the animals anesthetized with pentobarbital exhibited a considerably higher mean blood pressure prior to hemorrhage than the group IV dogs. The tendency of pentobarbital anesthesia to produce some elevation of blood pressure in dogs has been previously described by Corcoran and Page.[16] In addition, the fall of blood pressure following hemorrhage in the pento-

barbital group also exceeded that of the group IV animals. Thus, it appears that pentobarbital anesthesia may actually exaggerate the magnitude of post-hemorrhagic plasma dilution and that the effect is probably mediated through the influence of this anesthetic agent on blood presure.

The relationship between plasma dilution following hemorrhage and survival has long been of interest. It is true that in these studies the degree of plasma dilution was least in the group of animals (26–20° C.) with the lowest survival rate. On the other hand, in individual animals, this relationship was certainly not seen with any degree of consistency. However, it must be pointed out that the essential studies for the specific comparative evaluation of this problem under hypothermic and normothermic conditions have not yet been carried out.

SUMMARY

1. For the purpose of studying the response to severe but sub-lethal hemorrhage, a standard preparation was developed which involved rapid arterial hemorrhage of 35 per cent of measured blood volume in splenectomized dogs anesthetized with pentobarbital.

2. Using this preparation, a study of the effect of hypothermia on the survival rate following hemorrhage revealed a progressive diminution in tolerance as the body temperature was lowered below 31° C. The mortality rate was zero in normothermic animals, but was 82 per cent when body temperature was between 26 and 20° C.

3. Following hemorrhage, plasma volume rapidly increased by a shift of fluid into the intra-vascular compartment. At all temperatures, the maximum response was usually achieved within 30 minutes.

4. The amount of plasma volume increase was progressively less as body temperatures were reduced.

5. The correlation between the magnitude of the plasma volume change and the magnitude of the blood pressure change following the hemorrhage was remarkably close. It is suggested that the change in arterial blood presure may be a controlling factor of fundamental importance in regulating rapid plasma volume changes, irrespective of temperature.

6. In the warm animal, at least some, and usually most of the fluid which elevated plasma volume immediately following hemorrhage left the vascular compartment, usually within a period of one to three hours. The blood pressure returned toward normal during this same period when the plasma volume was falling. The dilution of the plasma, therefore, did not appear to be essential to the maintenance of blood pressure recovery following hemorrhage.

Note: The loyal assistance of Miss Dorothy Marco in conducting these experiments was invaluable and is gratefully acknowledged.

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DISCUSSION.—DR. FIORINDO ANTHONY SIMEONE, Cleveland, Ohio: These observations which Dr. Wilson and his associates have reported are truly very interesting from a number of points of view. I have been particularly interested in the hemodilution and the promptness of the hemodilution that has been reported.

Dr. Cannon prepared a monograph on traumatic shock following observations in World War I. One of the observations which disturbed him most, I know, was that hemoconcentration was found in the soldiers who had been traumatized. He stated in his monograph that that phenomenon was unexplainable on physiologic grounds.

One might say, then, that the reverse would be easily explainable, and I think such is the fact. The hemodilution is readily explainable on the loss of pressure. The dynamics within the capillary where hemodilution and hemoconcentration must occur, are altered in the direction of preventing excess loss from the arterial end of the capillary, favoring absorption of fluid from the venous end of the capillary. Hence, hemodilution would occur, and it would occur very rapidly because there are miles of capillaries and the effect should be actually demonstrable in one circulation time. So, the rapid hemodilution is what one would expect.

More difficult to explain, I think, is the loss of that hemodilution in a matter of an hour and a half to two hours, if I recall the charts correctly. That is considerably more difficult to explain, because the blood pressure is being maintained while oligemia persists. It must be maintained by the same mechanism that was operating at first. That is, an increased peripheral resistance, an increased arteriolar tone, with decreased pressure within the capillary route.

So, I imagine some other mechanism other than vasoconstrictor mechanism must be operating in the loss of the hemodilution. Just what this is, I believe, must await further data. It would be interesting to know what the kidneys are doing during that two- or three-hour period. It is possible that some fluid may be lost through that avenue to lose the hemodilution which had occurred very early.

I want to congratulate the authors for this truly excellent piece of work.

DR. FRANCIS D. MOORE, Boston, Massachusetts: I would also like to congratulate the essayists on a beautifully simple, clear demonstration. I would like to add one bit of information, and ask two questions.