Effect of Hypothermia in Irreversible Hemorrhagic Shock

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Irreversible hemorrhagic shock was studied in normothermic dogs and in dogs subjected to hypothermia at three different periods following the onset of the hemorrhage. A significant prolongation of life was observed in the hypothermic dogs, the increase in survival time being greatest in those dogs cooled early in the shock sequence. The temperature, pulse, respiration, blood pressure, electrocardiogram, rate of uptake of blood from a blood reservoir and autopsy findings in the two groups were noted.

Several investigators in the field of hemorrhagic shock have observed a lower mortality when their experiments were conducted during the winter than during the summer. Remington was unable to produce fatal hemorrhage in dogs in cool weather by withdrawal of 30 ml. of blood/Kg. body weight, whereas this degree of bleeding resulted in a 93 per cent mortality during the summer. This difference in mortality appears to be related primarily to the difference in temperature in the two seasons. Thus, Antos found a shorter survival period and a slightly higher mortality when he induced hemorrhagic shock in dogs during the summer than when the same procedure was performed on dogs who were cooled prior to the hemorrhage.

A lowered environmental or body temperature apparently increases the resistance of animals to hemorrhagic shock. Whether or not hypothermia would be beneficial to animals after the bleeding episode has not been clearly established. Blalock and Mason lowered the blood pressure of dogs to 75 mm. Hg by hemorrhage and then induced hypothermia in one half of the animals. They found, that although the application of cold did not increase the chance of survival, it did lengthen the period of survival by 5 hours. Cleghorn, on the other hand, using a similar oligemic shock procedure, and then placing the animals in environmental temperatures ranging from 52 F. to 95 F. noted optimal survival rates at 72 F. True hypothermia was not induced in the group at 52 F. as their rectal temperature averaged 101 F. (38.3 C.).

Little data is available on the effect of hypothermia in the therapy of so-called "irreversible" hemorrhagic shock. The present investigation was undertaken to test the validity of the hypothesis that dogs who were subjected to a hemorrhage which is usually irreversible would benefit by hypothermia as an adjunct to transfusion.

Method

A modification of Fine's technique was used for production of irreversible hemorrhagic shock. It allows for individual variation in the development of irreversibility and does not depend on a fixed period of hypotension. General anesthetic or analgesic drugs were not used, thus beneficial or deleterious effects of these agents on the shock state were avoided. All experiments were conducted in an air-conditioned operating room at a temperature of 73-75 F. Sterile technic was used and all instruments, cannulae, manometers, tubing and reservoirs were sterilized either by autoclaving or by soaking in zephiran chloride.

Under local procaine anesthesia both femoral arteries and one femoral vein of unselected, heparinized (2 mg./Kg. i.v.) mongrel dogs were cannulated. One cannula was connected to a reservoir bottle (containing an additional 1 mg./Kg. heparin) which was maintained at 52 cm. above the level of the artery, and the other arterial cannula was used for recording blood pressures. Blood pressure was recorded in mm. Hg at the higher pressures and in cm. of blood at the lower pressures for greater accuracy. The dog was bled into the Lamson reservoir, which acted as an arterial compensator, and the blood pressure became stabilized at 40 mm. Hg. Minor adjustments in the height of the reservoir

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were occasionally necessary to maintain this blood pressure. Frequent observations of pulse, blood pressure, respiration, volume of blood in the reservoir and electrocardiogram were made. Rectal temperatures were taken with either a continuous recording thermometer or a mercurial thermometer.

Since we were focusing on the problem of irreversible hemorrhagic shock we have chosen the point at which one third of the withdrawn blood had been taken up as the point of reinfusion. The blood remaining in the reservoir was filtered through gauze and reinfused through the cannula in the femoral vein.

Ten dogs were bled and reinfused according to the procedure outlined above. Twenty-one dogs were subjected to the identical procedure as the controls except that at various periods in the shock sequence they were rapidly shaved and cooled by immersion in a tank containing ice water at 4 C. When the dogs' rectal temperature had fallen to 32-34 C. the ice water was removed from the tank. The rectal temperature continued to fall, reaching a low of 25-30 C. (77-86 F.), the average being 27 C. If shivering occurred, it was controlled by giving a small amount of Nembutal (30-90 mg.) intravenously. Artificial rewarming using either warm blankets or warm water (at 35-40 C.) was employed in 7 cases when severe respiratory depression secondary to hypothermia seemed imminent. In these instances adequate respirations returned at a temperature of 29-31 C. and these dogs were then allowed to rewarm spontaneously, as were all the other dogs. The sex, weight, and maximum bleeding volumes were similar to those of the control group. Dogs alive after 10-12 hours were decannulated and returned to their cages.

Hypothermia was induced at one of the following three stages of shock: (1) during the progressive stage of normovolemic shock: 4 dogs; (2) at the time of reinfusion (i.e. at the one-third uptake point): 10 dogs; (3) during the impending or critical phase of oligemic shock (i.e., at 5-10 per cent uptake from the reservoir): 7 dogs.

RESULTS

Control Group. Figure 1 demonstrates the course of events in the average control experiment as correlated with the terms used by Wiggers1 to describe the various stages of irreversible shock. It illustrates the initial increase in volume of blood in the reservoir during the early phase of oligemic shock, followed by the progressive taking up of blood during the impending and critical phases. After the reinfusion of blood at the one-third uptake point, the dogs entered the normovolemic phase of hemorrhagic shock during which their blood volume was presumably at or only slightly less than normal.1 The blood pressure returned to normal ranges, remained there for a variable period of time and then gradually or suddenly fell until death ensued.

The average maximum bleeding volume of 50 ml./kg. body weight represents about 50 per cent of the total blood volume of the dog. The mean period of time from the onset of bleeding to the spontaneous take-up of one third of the shed blood was 3.6 hours. Death occurred on an average of 3.3 hours following the reinfusion (6.9 hours after the onset of bleeding). All dogs were dead within 91/4 hours from the beginning of the experiment.

Electrocardiograms of control dogs exhibited sinus arrhythmia (rate 70-90) prior to bleeding. After bleeding, the predominant findings were sinus tachycardia (rate 150-250), inversion of T waves, and RS-T segment depression. In one instance the RS-T segment was elevated. These changes would be interpreted by some as suggestive of myocardial ischemia. Reinfusion was followed by sinus slowing, initial normalization of the T waves, and usually a return of the RS-T segment to the isoelectric level. Terminally, atrial bradycardia or arrest, idioventricular pacemakers and ventricular tachycardia and fibrillation were noted.

![Fig. 1](http://circres.ahajournals.org/)

**Fig. 1.** The sequence of events in the average control experiment. Upper curve, arterial blood pressure (mm. Hg); lower curve, ml. of shed blood in reservoir. Classification of the various stages of irreversible hemorrhagic shock is that of Wiggers.1
Rectal temperatures fell 1-2 C. below the normal (37.5-40 C.) after bleeding, with a slight additional fall (0.5 C. or less) following reinfusion.

Autopsies revealed hemorrhages and congestion in the duodenum, small intestine, and occasionally colon; and contraction of the spleen. These findings have been noted by others in irreversible hemorrhagic shock.1

**Hypothermia Group.** Without exception, all of the hypothermic dogs survived longer following reinfusion than the mean of the control group. The degree of prolongation of survival time was greatest in those dogs cooled earliest in the shock phase and least in those cooled during the progressive phase of normovolemic shock (fig. 2).

Several of the dogs appeared sufficiently improved after hypothermia and reinfusion to suggest to the observers that they might have survived permanently had they been given additional supportive therapy. In this group were several dogs who were able to sit up in their cages and drink water long after the control animals were dead.

A slowing of the pulse rate occurred in the hypothermic state regardless of the stage of shock. Respiratory arrest secondary to the hypothermia did not occur at the lowest rectal temperatures in this series (mean temperature 27 C. with a range of 24.8 to 30.0 C.). This is probably related to the fact that general anesthesia was not used, since the same experiment performed in dogs under sodium pentobarbital anesthesia resulted in a greater tendency towards respiratory depression at these temperature levels.

In dogs cooled during or before reinfusion the blood pressure response to reinfusion was 10-15 mm. Hg lower than the controls. In the group cooled after reinfusion (group I) there was a slight transient rise in blood pressure on immersion, followed by a prompt fall to a level of 40-45 mm. Hg which was maintained until just before death.

In general, the electrocardiograms of the hypothermic dogs showed similar patterns to those of the controls but with the superimposition of effects known to be related to the hypothermia. These were: (1) sinus slowing with prolongation of the P-R, QRS, and QT intervals; (2) the appearance of an R' or notched R wave accompanied by prolongation of the QRS interval and suggestive of parietal left ventricular block and (3) a greater tendency for the persistence of diphasic or inverted T waves after reinfusion. The comparison of the electrocardiographic patterns of the control and the hypothermic dogs does not suggest an explanation of the apparent beneficial effect of hypothermia in prolonging the survival time of dogs in hemorrhagic shock.

As a rule, the hypothermic dogs exhibited a lesser degree of hemorrhage in the duodenum and small bowel at autopsy than did the controls. However, small areas of pulmonary atelectasis and congestion were common in the cooled group.

**Hypothermia During Progressive Stage of Normovolemic Shock.** Four dogs were bled as in the control group, reinfused at the one third uptake point, and when the secondary fall in blood pressure had reached 80-85 mm. Hg they were cooled. The average interval from transfusion to death was 5.4 hours or 2 hours longer than the same period in the control experiments* (fig. 2). However, there were no survivors.

**Hypothermia During Reinfusion.** Ten dogs were subjected to the same standard hemorrhage as the control dogs, but at the one third take-up point hypothermia was induced simultaneously with the reinfusion.

All of these dogs lived longer than the average control dog (fig. 2). Fifty per cent of the cooled dogs were alive 12 hours after the onset of the experiment; whereas none of the control dogs lived longer than 9 1/4 hours. One cooled dog was considered a permanent survivor and was sacrificed on the 10th postoperative day for autopsy study. The average time from transfusion to death in the remaining 9 dogs was 10 hours.

*The statistical significance of this increase in average duration of survival was evaluated by means of the t test, which yields exact probabilities for the difference between means of small samples. The derived value of t is 2.45, the probability, p, is between 0.01 and 0.05. A probability this low would generally be regarded as significant by statisticians.
POSTEL, REID AND HINTON 597

Fig. 2. Mean survival time following reinfusion of control dogs and dogs cooled at various stages of hemorrhagic shock. All dogs were reinfused when they had spontaneously taken up one-third of the blood in the reservoir. (In group III this occurred approximately 3 hours later than in the other three groups.)

was 8.4 hours, or over twice as long as the same period in the control group.*

Hypothermia during Oligemic Shock (at 5–10 per cent Uptake Point). Hypothermia was induced in 7 dogs after they had taken up 5–10 per cent of their maximum bleeding volume. This corresponds to the impending or critical phase of oligemic shock described by Wiggers1 (fig. 1). Three striking results were observed: (1) On immersion into the ice water there was a 5–15 min. period when blood flowed from the dog into the reservoir rather than in the reverse direction; (2) the rate of take-up of blood from the reservoir was slowed—the mean one third take-up point was 7.1 hours† or twice as long as in the control series; (3) following the reinfusion, which was given at the one third take-up point, a significant prolongation of life resulted.

The mean survival time following reinfusion was 13.1 hours‡ and the average total duration of life from the onset of bleeding was 20.2 hours as compared to 3.3 and 6.9 hours, respectively, in the normothermic group (fig. 2). All dogs were alive 12 hours after the onset of the ex-

* The t test of this difference in duration to death yields a value of 3.55; the probability, p, is less than 0.01. Statisticians would consider such a probability as indicating a highly significant difference.
† t is 4.91 which gives a p of less than 0.001.
‡ t is 5.14, yielding a p of less than 0.001.

periment, two were alive after 24 hours, but none survived permanently. An observation of interest in this group was the absence of shivering during the oligemic phase of shock. Shivering was noted only following the reinfusion of blood.

DISCUSSION

The results clearly indicate the beneficial effect of cooling hemorrhaged animals as early as possible. The mechanism by which the hypothermic state prolonged the survival time of dogs in hemorrhagic shock has not been determined.

Our results can be linked with previous observations that a lowered environmental temperature has both prophylactic and therapeutic value in experimental tourniquet and crush shock, and that death rates following ischemic shock caused by temporary occlusion of the aorta of dogs can be reduced by general body and visceral cooling. Evidence previously cited in this report suggests a beneficial effect of hypothermia in the prophylaxis of hemorrhagic shock. In the present study prolongation of life occurred when hypothermia was induced during and after an irreversible hemorrhage.

SUMMARY

Irreversible hemorrhagic shock was studied in 10 normothermic dogs and in 21 dogs subjected to hypothermia at three different periods following the onset of the hemorrhage. A statistically significant prolongation of life was observed in the hypothermic dogs, the increase in survival time being greatest in those dogs cooled early in the shock sequence.

Dogs cooled during the progressive stage of normovolemic shock lived two hours longer following reinfusion than did the controls. Hypothermia during reinfusion was associated with a survival time more than twice as long as the normothermic group and one dog survived permanently.

The induction of hypothermia during oligemic shock resulted in a significant prolongation of the uptake from the blood reservoir and a survival time four times as long as the control
EFFECT OF HYPOTHERMIA IN IRREVERSIBLE SHOCK

This prolongation of survival occurred despite the fact that the hypothermic group was maintained in a hypotensive state for a period twice as long as the normothermic dogs. Every one of the cooled dogs was alive 12 hours after the onset of the experiment, whereas all control dogs had succumbed before 9½ hours. There were no survivors in either group.

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SUMMARIO IN INTERLINGUA

Irrevertibile choc hemorrhagic esseva studiate in 10 canes normothermic e in 21 canes subjicitc a hypothermia a tres differente periodos post le declaration del hemorrhagia. Un statisticamente significative augmento de superviventia esseva observate in le canes hypothermic. Iste augmento esseva le plus marcate in canes in que le hypothermia esseva applicate tosto in le sequentia del choc.

Canes subjicite a hypothermia durante le stadio progressive de choc normovolemic viueva duo horas plus longe post re-infusion que le canes de controlo. Hypothermia durante le re-infusion esseva associate con un superviventia de plus que duple le superviventia in le gruppo normothermic e un can superviveva permanentemente.

Le induction de hypothermia durante choc oligemic resultava in un prolongation significative del introception ab le reservoir de sanguine e in un superviventia quatro vices illo del gruppo de controlo. Iste prolongation del superviventia occurreva in despecto del facto que le gruppo hypothermic esseva mantenite in stato de hypotension duo vices plus longe que le gruppo normothermic. Omne le canes del gruppo subjicite a hypothermia viveva 12 horas post le comenciamento del experimento, durante que omne le canes de controlo habeva morite ante le fin de 9½ horas. Il habeva nulle superviventes in o le un o le altre gruppo.

REFERENCES

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