Bleeding Volume Variations

1. Comparison of Effects of Halothane, Ether and Thiopental in Normal Dogs

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THIS investigation into the effects of anesthetic agents in the presence of acute hemorrhage was undertaken with two objectives. Firstly, we were interested in exploring the value of halothane for future use in this situation. Secondly, the employment of different anesthetic agents in experimental studies of acute bleeding has clouded past results because the effects of each agent have not received sufficient consideration. No experimental method for the evaluation of anesthetic agents used in the study of acute hemorrhage has been generally accepted. Techniques have been described by Wiggers [1] in 1950, Zweifach, *et al.*,[2] in 1952, Fine [3] in 1954, Zingg, *et al.*,[4] in 1958 and others. Walcott [5] in 1945 described the preparation that we have utilized, and he investigated it further subsequently.[6, 7] Its basic principles are as follows: The animal (dog) is bled rapidly through a femoral artery cannula until a definite end point is reached, described as a triad consisting of respiratory arrest, decerebration, and a change in the character of the stream of the shed blood from a steady one to one of a dripping nature. We have found the latter the most objective and constant and have used it to the exclusion of the others. The shed blood is collected, measured and rapidly reinfused. If the animal survives, one week later the same procedure is repeated and carried to the same end point with no attempt made to obtain survival. If both procedures are carried out under identical conditions, using local anesthesia, the amount of blood collected during the second bleeding will show excellent correlation. Each animal serves as his own control.

Lawson,[8] Walcott,[5] and Deniz and Gregersen [9] confirmed the constancy of the bleeding volume of the dog and also showed that it bore no direct relationship to the blood volume. Deniz and Gregersen [9] stated that "the bleeding volume may be looked upon as roughly defining the maximal agonal collapsibility of the circulatory system, or the maximal extent to which the system can shrink. Since the draining of the system to this point brings the circulation to a stop, bleeding could, in a sense, be considered as the effective functional fraction of the blood volume." As Lawson [8] has stated, the bleeding volume depends on "the volume and composition of the blood at the start of the bleeding; upon the amount of extravascular fluid which can be brought in, and the efficiency of mechanisms which maintain flow through vital organs, during the bleeding; and upon the ability of vital organs to survive reduction of the blood flow toward the end of the bleeding." Any desired variable can be introduced during the second bleeding and investigated for significance.

Method

The unanesthetized dog was placed in the supine position on an animal operating table. The femoral region was infiltrated with 1 per cent procaine, the femoral artery was exposed and incised and a bleeding catheter (constructed from plastic tubing according to the direction of Deniz and Gregersen [9]) was inserted one inch into the common femoral artery. The first 100 ml. of blood was collected into a 100 ml. siliconized-heparinized syringe and the remainder collected into one or two 500 ml. siliconized-heparinized graduates, depending upon the amount of shed

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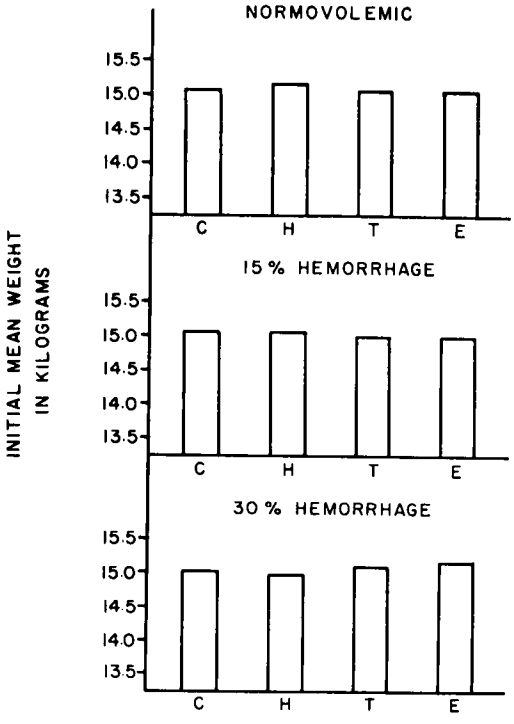

FIG. 1. Each upright bar represents the initial mean weight of nine animals. Bar *C* represents the control group, bar *H* the halothane group, bar *T* the thiopental group and bar *E* the ether group. There is no significant difference in the mean initial weights of any of the twelve groups.

blood. As the end point of the bleeding drew near, there was always a perceptible change in the dripping quality of the blood stream. This change always occurred after the cessation of respiration and decerebration of the animal. When the change was noted, dripping was allowed to continue for 30 seconds. Even when the end point was reached suddenly with a complete stoppage of the bleeding stream, a waiting period of 30 seconds was still observed.

The total amount of shed blood was measured, and immediately the first 100 ml. of shed blood were reinfused rapidly through the bleeding tube, the remainder was replaced as quickly as possible via the same route. The artery was ligated and the wound closed. The bleeding time and volume were recorded, the animal returned to his cage and fed a routine diet for a week. At the end of this period, the animal was returned to the laboratory and the entire procedure repeated, using the contralateral common femoral artery. In the control series, both bleedings were done under local procaine anesthesia. All general anesthetics were administered by two senior members of the anesthesia department. All experimental animals, including those under local anesthesia, received high flow rates of oxygen administered by means of well-fitting, canine face masks. Two per cent thiopental was introduced intravenously by syringe. Ether was administered by the open drop technique with a high flow rate of oxygen. Halothane was administered with a 10-liter permanent flow of oxygen through a Fluotec Mark II vaporizer with a concentration of 2 to 3 per cent for induction, then maintained with 1 to 1.5 per cent until a steady state was reached.

Each animal was deemed ready for bleeding when the respirations were regular and deep, at a rate of 18 to 26 per minute, and there was no evidence of cyanosis for a period of ten minutes. In addition, the inner canthal reflex was always present, and the outer canthal reflex was always abolished. To prove that animals in each anesthetic group were adequately oxygenated, randomly selected animals were reinfused with the shed blood after the end point had been reached. Each such animal recovered completely and was neurologically normal. In all groups of dogs, the femoral artery area was infiltrated with 1 per cent procaine. Random blood samples for anesthetic concentration were examined in dogs receiving ether and thiopental. Ether levels ranged from 43 to 95.5 mg./100 ml. with a mean of 60.1 mg./100 ml. Thiopental concentrations ranged from 7.8 μg. per liter to 16 μg. per liter with a mean of 10.7.

The experimental animals were divided into three groups of equal average weights (fig. 1). Each group was further subdivided into four subgroups. They were as follows:

Group 1—Normovolemic Dogs. (1) Nine dogs bled both times with local anesthesia (controls). (2) Nine dogs bled first with local anesthesia, secondly with halothane. (3) Nine dogs bled first with local anesthesia, secondly with thiopental. (4) Nine dogs bled first with local anesthesia, secondly with ether.

Group 2—Posthemorrhagic Dogs—15 Per Cent. The first bleeding was carried out as before. One week later, 15 per cent of the

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amount of blood collected during the first bleeding was withdrawn 30 minutes before the second bleeding volume determination. The second procedure was repeated as in group 1.

Group 3—Posthemorrhagic Dogs—30 Per Cent. The same procedure was followed as in group 2, except that 30 per cent of the first bleeding volume was withdrawn 30 minutes before the second bleeding volume determination, and then the procedure was performed as above.

Results

The close correlation of each of the nine dogs in the control normovolemic group is shown in figure 2. The open upright bar shows the amount of blood in milliliters per kilogram obtained in the initial bleeding in each dog. The striped bar depicts the amount of shed blood in milliliters per kilogram in the second bleeding of the same dog. The correlation coefficient is 0.863.

In the normovolemic group (fig. 3), it can be seen that, in the control animals, there was a slight gain of 1.6 ml./kg. of body weight in the second bleeding compared to the first. The halothane group showed a decrease of 1.4 ml./kg., the thiopental group a decrease of 3.6 ml./kg., and the ether group a decrease of 5.1 ml. per kilogram. These figures were subjected to statistical analysis using the analysis of variance method, and there is no statistically significant difference between any agent and the control group, or between any agent as compared to another.

In figure 4, the same method of analysis was used in the 15 per cent hemorrhage group. In the upper bar graph, the blood which was withdrawn prior to the actual commencement of the second bleeding is included. The lower graph does not include this initial amount of shed blood and is based upon the amount collected once anesthesia had been induced. As expected, this does not change significance in this group. If the amount of blood collected prior to the induction of anesthesia is included, the controls showed a decrease of 2.5 ml./kg., the halothane group 3.0 ml./kg., thiopental 0.0 ml./kg., and the ether group 6.0 ml./kg. If the previously withdrawn blood is not included, there is a decrease in ml./kg. of 12.0 for controls, 8.6 for thiopental, 11.2 for halothane and 15.4 for ether. Again, these figures show no statistically significant difference. However, if the values for ether at the 0 per cent and 15 per cent levels of hemorrhage are combined to increase the number of experi-

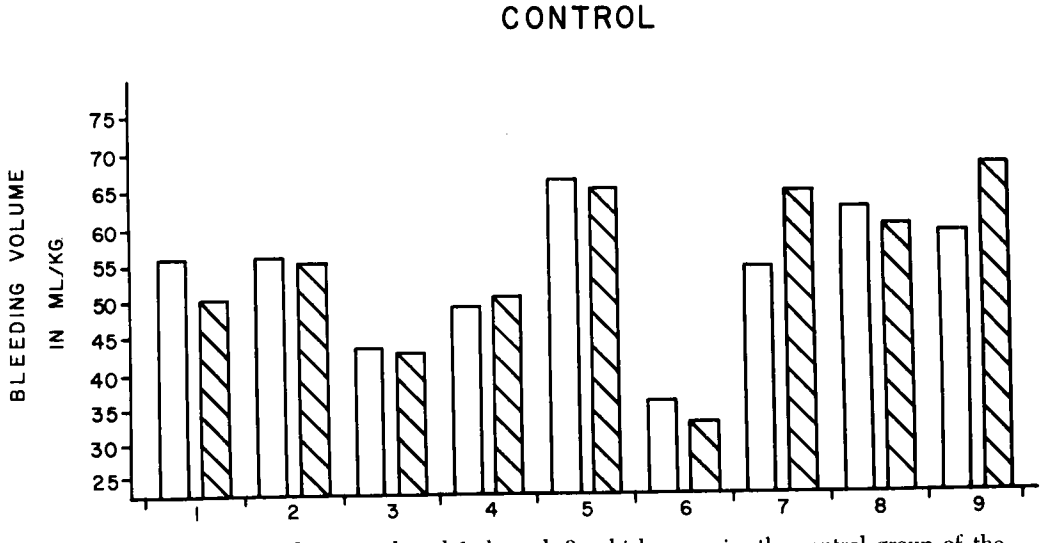

FIG. 2. Each of the dogs, numbered 1 through 9, which comprise the control group of the normovolemic series is shown. The open bar represents the shed blood obtained at the first bleeding in ml./kg. of body weight. The striped bar for each of the same dogs represents the amount of shed blood obtained one week later, again expressed in ml./kg. The correlation coefficient is 0.863.

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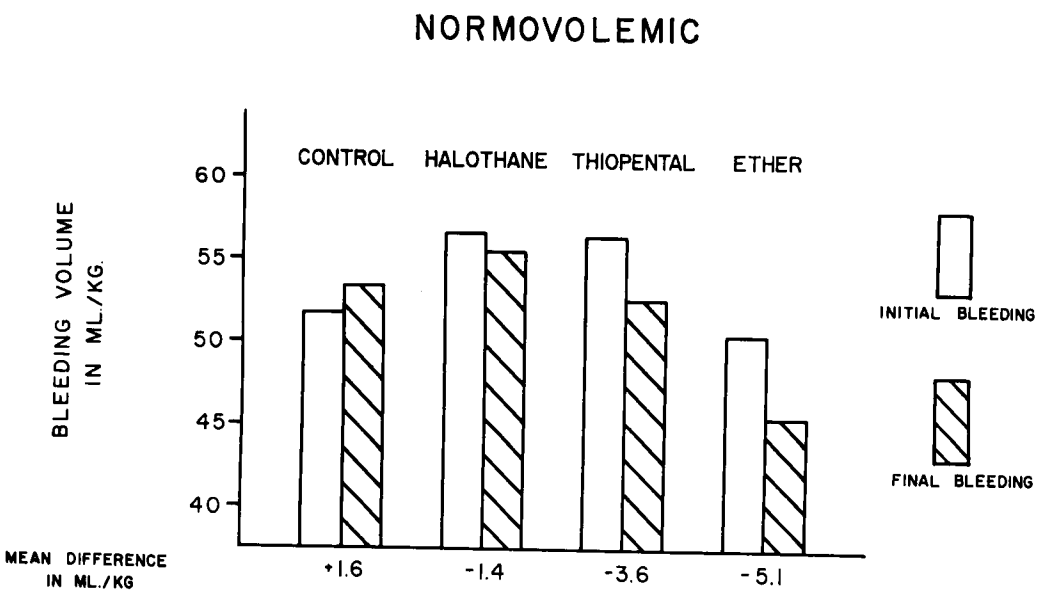

FIG. 3. Four groups of dogs are depicted. The first group is composed of the nine dogs bled under local anesthesia only. There was an increase of 1.6 mg./kg. in mean bleeding volume of the second bleeding (striped bar) over the first bleeding (open bar.) For all the other groups, there was a decrease in the bleeding volume on the second bleeding as compared with the first. Thus, when general anesthesia was given, there was less blood obtained than when the bleeding in the same dog was performed under local anesthesia alone.

mental animals, then ether is significantly different from the controls at the combined levels.

The 30 per cent hemorrhage group was examined in the same manner (fig. 5), and the results are as follows: If all blood collected is measured, the controls show a decrease of 0.6 ml./kg., thiopental an increase of 2.5 ml./kg., ether a decrease of 4.0 ml./kg. and halothane a decrease of 6.5 ml./kg. Disregarding the blood of the initial hemorrhage magnifies the figures but does not produce significant changes, and the controls are then decreased 20.1 ml./kg., thiopental 16.8 ml./kg., ether 23.6 ml./kg., and halothane 25.0 ml./kg. Halothane is significantly different from thiopental in this group.

Discussion

The normal response of the dog to acute hemorrhage is vasoconstriction, and since this preparation is 100 per cent fatal if blood is not immediately replaced upon reaching the end point, we must assume that the normal homeostatic mechanism does not protect the animal. Any agent or procedure, of whatever nature, that decreases the amount of blood that the animal can lose before this end point is reached must be classified as noxious. Since nothing has been tested thus far that will significantly increase this acute bleeding volume, then it follows that the instrumentality that produces the least decrease in the acute bleeding volume (in this instance, an anesthetic agent) would be the most advantageous. Recent publications have been tending toward this concept of protection from irreversible shock by the prevention of vasoconstriction. Boba and Converse [10] stressed this and developed the theme further in the clinical situation. They aimed at a delay or prevention of irreversible shock by the abolition of the usual vasoconstrictor mechanism. This concept has also been advanced by others and there is a sizable body of confirmatory data. Hakstian *et al.*[11] demonstrated almost complete protection against irreversible shock by the use of hydralazine (Apresoline), a moderately strong antihypertensive agent. They could only speculate on the mechanism of action and suggested that its function was in moderating the intensity of vasoconstriction or minimizing visceral damage due to anoxia. Deniz and Gregersen [9] made numerous attempts to increase the bleeding volume of the dog. Ex-

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perimental procedures utilized venous bleeding as compared to arterial, carotid-artery clamping, plasma expanders and epinephrine in single doses or continuous infusions failed to significantly alter the bleeding volume, and vagotomy significantly decreased it. All this tends to support our hypothesis that in this experimental preparation the best anesthetic in a given situation of acute hemorrhage is that agent which produces the least decrease in bleeding volume, since it would delay the onset of hemorrhagic shock the longest.

Halothane [12-14] has been found by many investigators to be a depressor of the cardiovascular mechanism. Some of this depression may have been due to excessive dosage due to inaccurate knowledge of halothane concentration being delivered. Systems in present use deliver an exact concentration of the drug. In spite of excellent control of dosage, reductions in cardiac output do result from inhalation of clinical concentrations of halothane.[15, 16] In addition, peripheral vasodilitation is marked [17] and adds to the hypotension already begun by the direct myocardial effects of the drug. This peripheral vasodilitation may be due to the localized action of halothane on the blood vessel wall [18] and by interference with the normal vascular response to catechol amines.[19] It is more likely due to release of normal neural vasoconstrictor tone, as it is abolished by nerve block.[17]

Because this agent was believed to be contraindicated in the presence of shock or in the actively bleeding patient,[20, 21] we elected this method of study to establish base levels in normal dogs. The other agents, ether and thiopental, were selected for comparison. With the base line changes established for this method of anesthetic evaluation, various changes from the normal physiologic state could be produced in the dog and possible adverse effects from these agents can be evaluated in the presence of each physiologic abnormality by the degree of change in the bleeding volume.

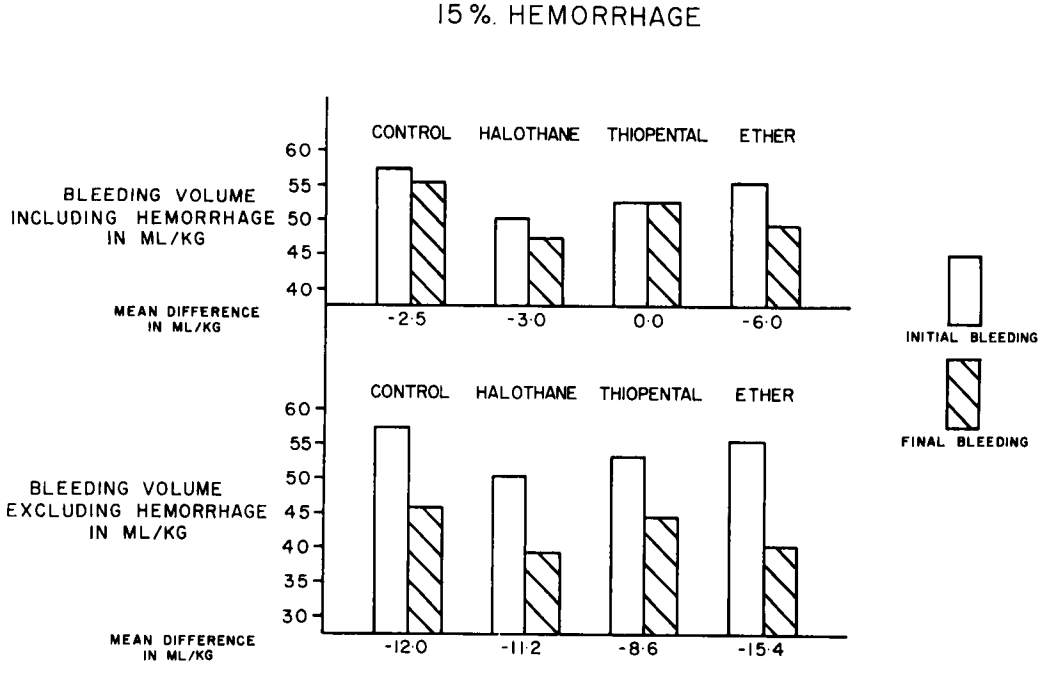

FIG. 4. Each group depicted consists of the mean values for nine dogs. The same groups are shown in two ways. In the upper portion, the blood removed before the induction of general anesthesia is added to that obtained during the general anesthesia and the result (striped bar) compared with the initial bleeding volume (open bar). In the lower portion, the blood removed prior to the second bleeding has not been added to the amount obtained at the second bleeding under anesthesia. Thiopental appears to be the best agent at this hemorrhage level, but is not significantly so.

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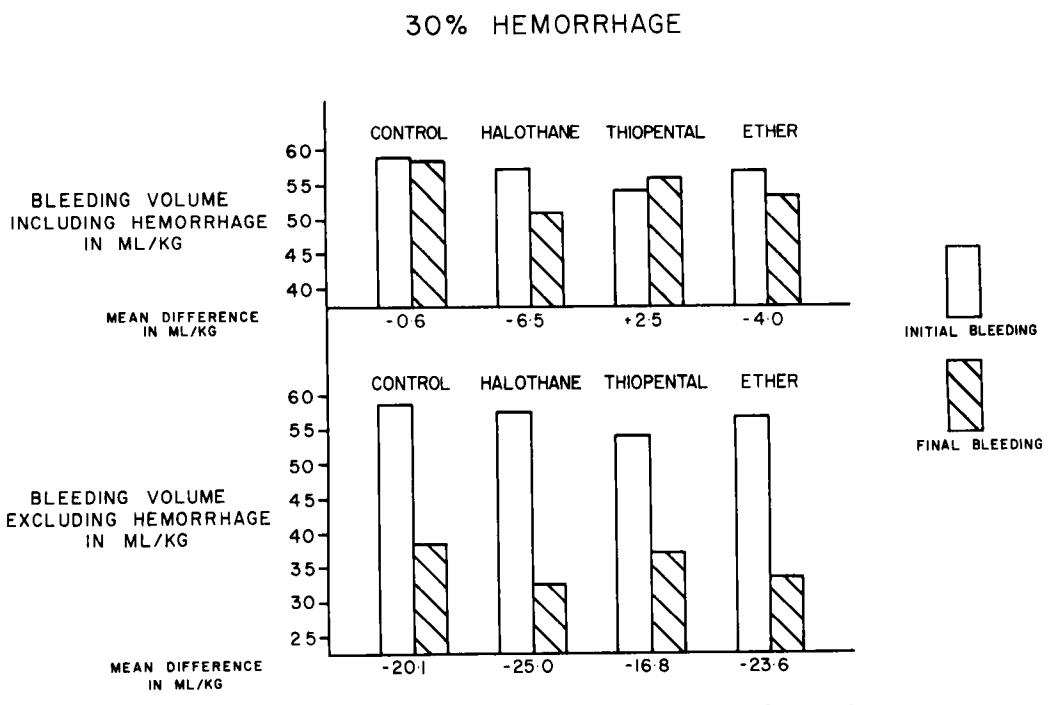

FIG. 5. Each group depicted consists of the mean values for nine dogs. The same groups are shown in two ways. In the upper portion, the blood removed before the induction of general anesthesia is added to that obtained during the general anesthesia and the result (striped bar) compared with the initial bleeding volume (open bar). In the lower portion, the blood removed prior to the second bleeding has not been added to the amounts obtained at the second bleeding under anesthesia. Thiopental appears to be the best agent at this hemorrhage level and is significantly better than ether.

If halothane anesthesia is accompanied by widespread vasodilitation and an increase in main organ blood flow,[17] it might be the agent of choice in clinical acute hemorrhage. Ether in light levels with a propensity for vasoconstriction would then be an undesirable agent to use. This seems to be borne out by the results of this experimental procedure. Recent work by Smith, Fabian and Carnes [22] employing a somewhat different experimental procedure compared the effects of cyclopropane with halothane and seems to confirm the belief that halothane is a satisfactory agent to be used in the presence of acute hemorrhage when compared to cyclopropane.

The result of the thiopental series is unexpected, and the best reference in support of this is that of Lum [23] who showed that, in a shock preparation that produced no survival, he was able to protect 12 dogs out of 20 by using pentobarbital anesthesia. It must be stressed that thiopental in this connection is thiopental without accessory anesthetic agents or adjuvants. As a generalized statement, our results indicate that in the normovolemic dog about to undergo acute hemorrhage or in the dog who has lost approximately 15 per cent of his bleeding volume before being anesthetized, ether would be the poorest agent to choose, and halothane or thiopental would be the most advantageous. In the experimental animal subjected to 30 per cent hemorrhage before having anesthesia induced, our results indicate that thiopental would be the anesthetic agent of choice, followed by ether and then halothane. Which parameter of the cardiovascular homeostatic mechanism is responsible for this differential in bleeding volumes we do not know. Crowell believes that the common parameter in hemorrhagic shock is oxygen debt.[24] In his studies, mortality increased directly as the oxygen debt increased. This factor did not influence the results of this series, as survival without neurological damage was the inevitable result in those dogs which were reinfused with the shed blood. It may

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be that the change in bleeding volume is caused by effects on the myocardium, on venous return, peripheral vasoconstriction, splenic contraction, sympathetic tone or capillary permeability, either singly or in various combinations. Further experimentation may elucidate the facet responsible for the changes noted.

Summary and Conclusions

The constancy of the acute bleeding volume of the dog was confirmed and is reproducible. The acute bleeding volume is an experimental model which, when used as described, reveals differences in the effects of various anesthetic drugs. The exact mechanism involved in producing this differential in acute bleeding volume is not known to us at this time.

No anesthetic drug tested increased the acute bleeding volume significantly in the normovolemic dog, and ether produced the greatest decrease, followed by thiopental and halothane.

In the 15 per cent hemorrhagic group, ether produced the greatest decrease, followed by halothane and thiopental. In the 30 per cent hemorrhagic group, halothane produced the greatest decrease, followed by ether and thiopental.

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