EFFECT OF HALOTHANE ANAESTHESIA AND HYPOTHERMIA ON SURVIVAL OF DOGS SUBJECT TO ACUTE UNTREATED HAEMORRHAGE

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SUMMARY

The effect of halothane anaesthesia on the survival of bled animals was investigated in seventy-one dogs divided into three groups. In all dogs 40 ml/kg of arterial blood was taken out, this being followed 1 hour later by an additional haemorrhage of 10 ml/kg. Shed blood was not re-transfused and substitution for it was not carried out. Halothane anaesthesia alone and combined with cooling was applied after the first haemorrhage. The greatest survival rate (66.6 per cent) was found in the control (unaesthetized) group, and the least (22.8 per cent) in dogs bled under halothane anaesthesia. The survival rate was insignificantly lower (59.1 per cent) in dogs cooled under halothane than in the control group. It is concluded that the adverse effect of halothane anaesthesia was counterbalanced by hypothermia.

The rationale for the use of hypothermia after an acute haemorrhage, in order to prevent or delay irreversible damage to vital organs, has not been definitely established to date. One of the problems that arose from our earlier investigations (Pantelic et al., 1960; Pantelic and Vajs, 1962) related to the undesirable effects of the anaesthetics used (thiopentone or chloralose). Our first series of experiments with halothane started in 1962 and at that time the influence of the hypotensive action of halothane on the survival in severely bled animals was uncertain (Smith, Fabian and Carnes, 1961). In 1962 there appeared two papers by Freeman (1962a, b) who was unable to demonstrate a deleterious effect of halothane anaesthesia due to its hypotensive action. The problem of the effect of halothane on the survival of bled animals was then shifted to an effect on pulmonary ventilation. Freeman (1962b) and Freeman and Nunn (1963) concluded that it is necessary to add oxygen to the inspired air to counterbalance the adverse effects of halothane anaesthesia.

In the present study a different technique of haemorrhage was used: halothane was the only anaesthetic, and hypothermia was employed in place of additional oxygen.

METHODS

The experiments were performed on seventy-one mongrel dogs of both sexes, weighing between 10 and 21 kg. There were three groups of experiments.

Control group. There were twenty-seven dogs in this group. Under local anaesthesia (1 per cent procaine) the femoral vessels on both sides were exposed. Heparin 2 mg/kg was injected intravenously. By means of a mercury manometer blood pressure was measured in a cannulated artery and continuously monitored on a smoked drum paper. From the other cannulated femoral artery 40 ml/kg of blood was withdrawn at an average rate of 100 ml/min. This was followed 1 hour later by an additional haemorrhage of 10 ml/kg when heparin (2 ml/kg) was again injected. The shed blood was not retransfused. All surgical work and injections were carried out with an aseptic technique. In animals alive 1 hour after the second haemorrhage, the exposed blood vessels were ligated, the wounds sutured and then they were transferred to their cages. Dogs were allowed to drink water but food was not given for 24 hours before and after haemorrhage. Heart rate (e.c.g.) and rectal temperature (thermocouple) were recorded frequently during the experiments. Respiratory movements were monitored (Marey's capsule) simultaneously with blood pressure. The venous haematocrit was determined before bleedings, at 1 hour after the second haemorrhage, and at 24 hours after the first haemorrhage.
**Halothane group.** Twenty-two dogs were used. The procedure was the same as in the control group except that at 5 minutes after the first haemorrhage halothane anaesthesia was induced over 3–5 minutes and thereafter maintained for various lengths of time. Before endotracheal intubation halothane was given by facepiece and then subsequently a non-rebreathing system was used with room air as the carrier gas. A fixed concentration of halothane was not given but an attempt was made to maintain stage III, plane 1–2 anaesthesia. If the state of an animal deteriorated (sudden fall in arterial pressure and slowing of respiration) either the level of anaesthesia was reduced or anaesthesia discontinued. In these cases, however, there was no recovery of arterial pressure, death occurring in the same manner as in the control animals—that is, respiration ceased and soon after that cardiac arrhythmia ended in ventricular fibrillation. Respiration was not assisted at any time during the experiments.

**Hypothermic group.** Twenty-two dogs were used. In this group, immediately after anaesthesia was induced, the previously shorn dog was covered with crushed ice and cooled until the rectal temperature fell to 32°C. This took approximately an hour. Otherwise, the experimental procedure was the same as in the two previous groups. Cooled animals were allowed to rewarm spontaneously and only when rectal temperature dropped below 29°C was rewarming assisted with electric lamps placed above the chest and abdomen.

Postmortem examinations were done on most of the dogs that died.

**RESULTS**

**Survival.**

Data presented in table I show that the highest survival rate was in the control group (66.6 per cent), insignificantly lower (59.1 per cent) ($\chi^2 = 0.062; P > 0.70$) in dogs cooled under halothane anaesthesia; in the halothane group, however, only 22.8 per cent of dogs survived.

Results of postmortem examinations did not show great differences in dogs from the various groups.

**Arterial pressure variations.**

In the dogs in all groups, the fall in arterial pressure during the first bleeding was greater in dogs that died, viz. to an average of 21.4 per cent of the control value as compared with 33.6 per cent in the surviving dogs. This difference was highly significant ($t = 4.4; P < 0.001$).

Induction of halothane anaesthesia caused a variable fall in arterial pressure, but after about 10 minutes, that is with the stabilization of anaesthesia, there was a steady rise of arterial pressure in nearly all dogs (fig. 1). Soon after discontinuation of anaesthesia the arterial pressure usually started to rise further and in some dogs it was a very marked rise, except in the cases in which the state of the animal deteriorated during anaesthesia.

As shown in figure 1, the lowest arterial pressures in the halothane group were in ten dogs which died during the first hour after the second haemorrhage. Only in one of these ten dogs was anaesthesia discontinued before the second haemorrhage and in about 5 minutes his arterial

**Table I**

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Number of dogs</th>
<th>Survived</th>
<th>Died</th>
<th>Time of survival (hours)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27</td>
<td>18(66.6%)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Halothane</td>
<td>22</td>
<td>5(22.8%)</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Halothane and hypothermia</td>
<td>22</td>
<td>13(59.1%)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>36</td>
<td>35</td>
<td>19 15 1</td>
</tr>
</tbody>
</table>

* Died within 1, 24 and 48 hours respectively of the end of the second haemorrhage.
Changes (mean values) in blood pressure, heart rate and rectal temperature. Zero time is the end of the first haemorrhage. Arrows indicate the end of the second haemorrhage.

**FIG. 1**

Blood pressure variations immediately before and after second haemorrhage.

**Halothane group:**
- ▲—dogs bled under anaesthesia.
- △—dogs unanaesthetized at that time.
- ○—Control group.

**Hypothermic group:**
- ■—dogs bled under anaesthesia.
- □—dogs unanaesthetized at that time.
pressure rose from 32 to 72 mm Hg. In the halothane group as a whole anaesthesia was discontinued before the second haemorrhage in eight dogs, only two of which survived.

In the hypothermic group the rectal temperature dropped to 32°C and anaesthesia was discontinued before the second haemorrhage in four dogs, all of which died (fig. 1). The surviving dogs cooled more slowly (60–115 minutes) and on average reached this level of hypothermia in about 20 minutes after the second haemorrhage.

Figure 2 shows the mean arterial pressures of individual dogs immediately before and after the second haemorrhage. It is apparent that the arterial pressures in the majority of dogs bled under halothane were significantly lower than those in dogs not receiving halothane at that time (t = 7.7; P < 0.001 before haemorrhage; t = 2.8; P < 0.01 after haemorrhage). However, among dogs bled under halothane there was not a statistically significant difference between the means of arterial pressures in the surviving dogs and those which died (t=1.6; P>0.1).

In survivors and in dogs that died, the average arterial pressure fall during the second haemorrhage was less in the anaesthetized than in the unanaesthetized dogs, these differences being highly significant (t=5.6, P<0.001 for survivors and t=5.9, P<0.001 for dogs which died).

Arterial pressure variations after the second haemorrhage are shown in figure 1. In the halothane group, three of the five dogs which survived were under anaesthesia up to 1 hour after the second haemorrhage. Only two of seven dogs which survived more than 1 hour after the second haemorrhage were under anaesthesia for some time after the second haemorrhage. Nevertheless, their arterial pressures were significantly lower (fig. 1) than those of the survivors. After discontinuation of anaesthesia there was no recovery of arterial pressure in any of the dogs which died.

In cooled dogs which survived, the interruption of anaesthesia after the second haemorrhage was followed by a steady rise of arterial pressure whereas this occurred only in two out of nine dogs which died.

At the end of 1 hour after second bleeding fifty-two dogs were still alive. Thereafter no animal received halothane. The arterial pressures at that time (anaesthesia discontinued at least 10 minutes earlier) were below 60 mm Hg in fourteen out of sixteen dogs which died later on but also in ten out of thirty-six dogs which definitely survived (fig. 3). Only one dog having an arterial pressure greater than 60 mm Hg died, this being a hypothermic animal with the lowest rectal temperature (28.3°C). This dog died 5 hours after
second haemorrhage without spontaneous rise in temperature.

**Heart rate variations.**

Due to the high concentrations of halothane given during induction of anaesthesia the post-haemorrhagic acceleration of cardiac rate was at first impeded, but with the stabilization of anaesthesia a steady increase in cardiac rate occurred simultaneously with the rise of arterial pressure. Nevertheless, the degree of compensatory tachycardia was lower in anaesthetized dogs and the interruption of halothane anaesthesia was followed by an increase of cardiac rate. In the hypothermic group cooling was another factor tending to slow the cardiac rate; the lower the temperature the greater its influence. This may account, at least partly, for the lowest heart rates seen after second haemorrhage in the cooled dogs which died (fig. 1).

**Respiratory rate variations.**

The majority of dogs from the control group were rather restless throughout the experiment, even after the second haemorrhage when arterial pressures were lower. There was no obvious difference in the behaviour of surviving animals and those which died. When arterial pressures were very low, e.g., 40 mm Hg, the dogs were quiet, with the respiratory rates varying from 16 to 80 b.p.m.

In the anaesthetized dogs wide variations in respiratory rate were also seen. Usually there was a rise after induction of anaesthesia but in some dogs the effect was quite different. However, the slowing of respiration due to halothane occurred both in some dogs which survived and in some which died.

In cooled dogs at temperatures of 30°C or below respiration was further slowed.

**Table II**

**Haematocrit variations.**

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Before first haemorrhage</th>
<th>Before second haemorrhage</th>
<th>1 hr. after second haemorrhage</th>
<th>24 hrs. after haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs which survived</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>R: 32-62</td>
<td>28-58</td>
<td>24-55</td>
<td>21-40</td>
</tr>
<tr>
<td>M±SD</td>
<td>52.7±5.0</td>
<td>48.3±6.2</td>
<td>44.1±4.5</td>
<td>32.3±5.4</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>91.6</td>
<td>83.6</td>
<td>61.2</td>
</tr>
<tr>
<td>Halothane group</td>
<td>R: 47-52</td>
<td>44-50</td>
<td>41-48</td>
<td>27-45</td>
</tr>
<tr>
<td>M±SD</td>
<td>49.0±2.0</td>
<td>45.7±2.8</td>
<td>43.0±3.6</td>
<td>37.0±8.9</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>93.2</td>
<td>87.7</td>
<td>75.5</td>
</tr>
<tr>
<td>Hypothermia group</td>
<td>R: 42-57</td>
<td>34-50</td>
<td>34-48</td>
<td>26-40</td>
</tr>
<tr>
<td>M±SD</td>
<td>49.8±6.0</td>
<td>45.1±5.3</td>
<td>41.2±5.1</td>
<td>33.6±4.9</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>90.5</td>
<td>82.7</td>
<td>67.4</td>
</tr>
<tr>
<td>Dogs which died</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>R: 31-58</td>
<td>31-55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M±SD</td>
<td>48.6±8.2</td>
<td>44.5±7.9</td>
<td></td>
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</tr>
<tr>
<td>N</td>
<td>9</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>91.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane group</td>
<td>R: 36-58</td>
<td>30-58</td>
<td>28-38</td>
<td></td>
</tr>
<tr>
<td>M±SD</td>
<td>46.8±6.8</td>
<td>40.6±4.7</td>
<td>35.6±3.9</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>86.7</td>
<td>76.0</td>
<td></td>
</tr>
<tr>
<td>Hypothermia group</td>
<td>R: 49-55</td>
<td>42-56</td>
<td>30-45</td>
<td></td>
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<tr>
<td>M±SD</td>
<td>50.0±4.1</td>
<td>44.4±5.6</td>
<td>37.7±6.1</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>88.8</td>
<td>75.4</td>
<td></td>
</tr>
</tbody>
</table>

R=range; M±SD=mean value with a standard deviation; N=number of dogs; %=percentage of the mean value before the first haemorrhage.
Haematocrit variations.

A more marked drop of haematocrit occurred after the second haemorrhage, this being especially seen in dogs which died (table II). Haemodilution continued in the next 24 hours.

The greater drop of haematocrit value after the first haemorrhage in the anaesthetized dogs which died than in dogs of the control group was not statistically significant ($t=1.35; P>0.1$). However, at 1 hour after second bleeding the lowering of a haematocrit was significantly greater ($t=3.56; P<0.001$) in dogs which died as compared with that in the survivors (only dogs from the halothane and hypothermic group are taken into account).

DISCUSSION

There are many factors affecting survival of an untreated animal after haemorrhage, the amount of blood withdrawn being predominant. In these experiments bleeding volume was the same in all dogs, e.g., 50 ml/kg body weight. It is well known, however, that this does not mean the same percentage reduction of the circulating blood volume in all dogs. According to available data (Gorbunova, 1957; Swan et al., 1959; Klütsch et al., 1962), blood volume in normal dogs varies from 70 to 100 ml/kg body weight. Therefore, the percentage reduction of circulating blood volume after withdrawal of a fixed amount of blood may differ by as much as 30 per cent. Since blood volume determinations were not undertaken it is difficult to state how much this factor accounted for the highest mortality rate in the halothane group. All dogs were apparently in good health and not selected for any of the three groups. In any standard bleeding procedure wide individual variations in biological susceptibility are generally recognized.

Some dogs were quiet before and during haemorrhage, the others restless. We could not establish that this affected survival. Sex differences seem not to be of importance for survival, either.

As may be seen from figure 3 the arterial pressures before the first bleeding were high in the majority of dogs. According to Katz, Skom and Wakerlin (1957), $145 \pm 7.5$ mm Hg could be taken as the upper limit for the normal mean arterial pressure (femoral artery) in the trained, unanaesthetized mongrel dogs. In our laboratory, however, under similar conditions, somewhat higher values, i.e. $148 \pm 11.3$ mm Hg have been found. It seems, therefore, that the majority of dogs in the present series of experiments were slightly hypertensive ($152 \pm 12.5$ mm Hg) and especially those which died ($155.8 \pm 11.2$ mm Hg). Although these differences of the levels of arterial pressures are not statistically significant the influence on the survival should not be neglected. Taking the value of 160 mm Hg (our laboratory finding) as the upper limit for the normal mean arterial pressure, it follows that only seven out of thirty-six dogs which survived had initial arterial pressures above this level compared with fifteen out of thirty-five dogs which died.

Fig. 4
Duration of halothane anaesthesia.

The greater fall in arterial pressure during the first haemorrhage occurred in dogs which died. Several factors might be operating in producing this effect; for example, variations in reduction of circulating blood volume, rate of bleeding, degree of compensatory vasoconstriction, and perhaps influence of high initial arterial pressure.
It is interesting to note the greater fall in arterial pressure due to second haemorrhage in the unanaesthetized dogs, but it is impossible to state anything conclusively about the nature and meaning of this phenomenon.

Anaesthesia lasted from 30 to 115 minutes but there was no relationship between duration of anaesthesia and survival of animals (fig. 4). Although the average duration of anaesthesia was nearly the same in the halothane group (72 min) and the hypothermic group (70 min), the survival rate was far greater in the latter.

As shown in figure 1 there was not a great difference between the arterial pressures in dogs of the halothane and hypothermic groups. This is in accordance with our previous experience that cooling to a rectal temperature of 32°C does not markedly affect the spontaneous rise of arterial pressure in dogs after bleeding (Pantelic and Vajs, 1962). In these earlier experiments, in which chloralose anaesthesia was used, a beneficial effect of hypothermia induced in dogs after a severe haemorrhage was not clearly evident, at least as far as the survival of animals is concerned. Therefore, a beneficial effect of hypothermia in the presented experiments is only suggestive and relative to a deleterious effect of halothane anaesthesia.

Freeman (1962) could not demonstrate an adverse effect of halothane due to its hypotensive action on dogs subjected to controlled posthaemorrhagic hypotension. Because addition of oxygen to the inspired air resulted in greater survival of animals, he suggested that inadequate arterial oxygenation due to impaired pulmonary ventilation is the serious disadvantage of halothane anaesthesia in haemorrhaged animals. Detailed study (Freeman and Nunn, 1963) showed that the great increase in physiological deadspace is the mechanism by which halothane anaesthesia acts unfavourably in severely bled animals.

Since we have no data concerning pulmonary ventilation and arterial blood oxygen saturation, we cannot say whether this mechanism was operated in the halothane group of our experiments and thereby resulted in the greatest mortality rate seen in this group. However, as there is a tendency for the anatomical and physiological deadspace to be increased in hypothermia, and since we did not enrich the oxygen content in the inspired air, the primary mechanism of beneficial action of hypothermia in the present experiments might be other than that related to blood oxygenation in the lung.

CONCLUSIONS

The majority of the unanaesthetized dogs survived in spite of the fact that the acute blood loss amounting to 50 ml/kg had not been substituted.

Induction of halothane anaesthesia after initial haemorrhage (40 ml/kg) was followed by death in the majority of dogs no matter whether the second haemorrhage (10 ml/kg) was done in the anaesthetized dogs or not and irrespective of how long the anaesthesia lasted (30–115 min).

Mild hypothermia (cooling to 32°C of rectal temperature) induced after the first haemorrhage markedly increased the survival rate of animals anaesthetized with halothane.

REFERENCES


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L'EFFET DE L'ANESTHESIE PAR L'HALOTHANE ET DE L'HYPOTHERMIE SUR LA SURVIE DE CHIENS SOUMIS A UNE HEMORRAGIE AIGUE NON TRAITEE

SOMMAIRE

L'effet de l'anesthesie par l'halothane sur la survie d'animaux saignes a ete examine chez 71 chiens divisies en trois groupes. Chez tous les chiens 40 ml/kg de sang arteriel a ete retire, cette saignee etant suivie une heure plus tard par une hémorragie supplementaire de 10 ml/kg. Le sang enleve n'a pas ete retransfus et aucune substitution n'a ete faite. L'anesthesie par l'halothane seule ou combinee au refroidissement a ete appliquee apres la premiere hémorragie. Le taux de survie le plus important a ete trouve (66,6%) chez le groupe de controle non anesthesie, et le taux le plus bas (22,8%) chez les chiens saignes sous anesthesie par l'halothane. Le taux de survie etait plus bas d'une facon insignifiance (59,1%) chez les chiens refroidis sous halothane par rapport au groupe de controle. On conclut que l'effet defavorable de l'halothane a ete contrebalance par l'hypothermie.

EDITORIAL—continued

While the clinical significance to anaesthesia in the broad sense is by no means clear it is inviting to speculate upon the possibility that other toxic effects of drugs may be explained by as yet undiscovered genetic polymorphisms. It follows also that such possibilities must be taken into consideration in the design of trials of new and potent drugs, and also in the investigation of cases of drug toxicity. It would appear that closer attention will be needed to exclude genetic abnormalities affecting drug metabolism when attempting to control the conditions under which drug investigations are carried out.

Taking into consideration the ever-widening range of extremely potent drugs currently used in all branches of medicine, and noting the increasing frequency of the use of these drugs in patients coming to surgery, the argument for simplicity in anaesthetic technique has even greater appeal.