The Effects of Ether Anesthesia for Surface-Induced Hypothermia on Cardiopulmonary Function in the Dog

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SUMMARY

The effects of the depth of ether anesthesia for surface-induced hypothermia on hemodynamics and blood gas were experimentally studied in the adult Beagle dogs. The dogs were classified into 3 groups according to the depth of ether anesthesia; group I (middle), group II (deep), and group III (light). Severe arrhythmia was found in groups II and III, and 6 dogs (66.7%) of group II died of ventricular fibrillation or standstill. During hypothermia, hemodynamic changes of groups I and II were significantly milder than those of group II. Aortic mean pressure of group I was maintained higher than that of group III, and the difference was especially significant at the esophageal temperature of 20°C (p<0.01). From these results, the ether anesthesia in group I seemed to be superior to that of other groups. Under this level of ether anesthesia, the mean blood ether concentration was 153 mg/dl at the esophageal temperature of 20°C. Moreover, because a good correlation was noted between blood pH or BE and blood ether concentration, it seemed that they were better indicators of the depth of ether anesthesia.

Key words: blood ether concentration, blood gas, ether anesthesia, hemodynamics, surface-induced hypothermia.

INTRODUCTION

In human heart surgeries, the surface-induced hypothermia was replaced by the cardiopulmonary bypass system. In canine heart surgeries, however, the surface-induced hypothermia is still useful because it is well suited to small-sized dogs, inexpensive, and simple to perform. In the past, surface-induced hypothermia techniques using various kinds of anesthetic agents, such as thiopental sodium, morphine, fentanin, NLA, halothane, azeotrope, isofluren, and others were reported. They were almost
always experimentally used, and were hardly applied in clinical trials due to unstable results. However, surface-induced hypothermia with ether anesthesia has been used in many clinical cases because of its wide safety in the anesthetic phase, stable hemodynamics and antiarrhythmic effects. In the majority of such studies, deeper ether anesthetic phase was used for surface-induced hypothermia, however the depth of ether anesthesia was decided empirically rather than the scientific background. Although there have been a few reports on the depth of ether anesthesia through measuring blood ether concentrations, the measurement requires the complex procedures. Recently, the modern and simpler methods such as gas chromatography or infra-red analysis have become available, which may enable to assess the reliable blood ether concentration during the anesthesia.

The purpose of this study was to clarify the optimal anesthetic phase of ether anesthesia for hypothermia and blood ether concentrations from the aspect of cardiopulmonary functions.

MATERIALS AND METHODS

Nine adult Beagle dogs of both sexes with the body weight ranging from 6.6 to 9.0 kg (mean, 8.4 kg) were used in this experiment with a cross-over design. The dogs were classified into 3 groups according to the depth of ether anesthesia; I (middle), II (deep), and III (light) groups. They were used all the three experiments above at a 7-day interval. The same dog received the different depth of ether anesthesia in the order of I·II·III (3 dogs), II·III·I (3 dogs), and III·I·II (3 dogs), respectively. All the experiments were performed under the guidelines for animal care of School of Medicine, Nagoya University.

Hypothermia technique: The details of our method of surface-induced deep hypothermia in the dog have been reported previously, and summarized in the protocol of hypothermia techniques (Fig. 1). The premedication drugs used were shown in Table 1. Anesthesia was induced with thiamylal sodium (1.25-1.9 mg/kg body weight, iv) and the animals were intubated. Ether was inhaled with an in-circuit wick type vaporizer in a closed circuit. Pancuronium bromide at a dose of 0.04 mg/kg was injected intravenously before the beginning of ether anesthesia. The dogs were then ventilated with an in-circuit respirator (AR300, Acoma, Tokyo) in a closed circuit. Pancuronium bromide at a dose of 0.04 mg/kg was injected intravenously before the beginning of ether anesthesia. The dogs were then ventilated with an in-circuit respirator (AR300, Acoma, Tokyo) at a tidal volume of 15 ml/kg and a respiratory rate of 20 breaths per minute. The dogs were then covered with a plastic sheet, and cooled by immersing them in ice water at the end of the second ether stage (defined in the following ether anesthesia). After the esophageal temperature (ET) reached 20°C, the dogs were immediately rewarmed by immersion in circulating
Fig. 1. Protocol of hypothermia.
(See the method)

Table 1. Premedication drugs.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Before induction</th>
<th>1 h</th>
<th>30 min</th>
<th>10 min cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Acepromazine</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
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<tr>
<td>Atropine</td>
<td>0.025</td>
<td>0.025</td>
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Hot (42°C) water. Ten percent low molecular weight dextran in saline solution (10 ml/kg/hr) was infused with dexamethasone (4 mg/kg) during cooling, followed by lactated Ringer solution (10 ml/kg/hr) infusion.

Ether anesthesia: The ether anesthesia was classified into three stages: the first (induction), the second (maintenance until beginning of cooling) and the third (maintenance during cooling). The depth of ether anesthesia (I, II and III) was divided based on ether consumption. In group I (middle), vaporizer dial was set at 1.5, and 1 ml/kg of ether was inhaled at the first stage, total 2 ml/kg at the second stage and total 3 ml/kg at the third stage, respectively. In group II (deep), the dial was set at 2, and the inhaled ether volume was twice that of group I at each stage. In group III, the dial was set at 1, and the inhaled ether volume was half that of group I at each stage. The ether was immediately stopped upon completion of the third stage and not washed until ET recovered to 30°C during rewarming.

Measurements: A 6 or 8 Fr catheter for arterial pressure and a 5 Fr Swan-Gantz catheter for pulmonary arterial, pulmonary capillary wedge and central venous pressure were inserted either from the carotid artery and jugular vein, or the femoral artery and vein, respectively. These pressures as well as electrocardiogram and cardiac output (using the thermodilution method) were monitored and recorded (Life Scope 9 and Thermal Array Recorder, Nihon Kohden, Tokyo).
Fig. 2. Changes in blood ether concentration of three groups during hypothermia.
I : Group I , II : Group II , III : Group III

Arterial blood samples for measuring blood gas and ether concentration were collected before ether anesthesia, at the end of the first and second ether stages, when ET was 30°C, 25°C and 20°C during cooling, and when ET was 25°C, 30°C, and 35°C during rewarming (Fig. 1). Blood gases were measured at 37°C with an acid-base auto-analyzer (ABL30, Radiometer, Tokyo) without temperature correction. ET and rectal temperature were monitored with a telethermometer (Finer CTM 303, Terumo, Tokyo). Urine volume was monitored as an index of peripheral circulation with a balloon urethral catheter inserted into the bladder.

The blood ether concentration was determined by the n-Hexane extraction method, using a gas chromatography (GC) (GC-15A, Shimazu, Tokyo) equipped with a flame ionization detector (FID). Standard ether blood samples were prepared by adding 1, 2, 3, 4, or 5 µl ether to 1 ml arterial blood in a 2-ml vacuum sampling tube. These standard samples and blood samples collected from the experimental dogs were then mixed with 1 ml n-Hexane, shaken vigorously for 15 minutes, and centrifuged at 3500 rpm for 10 minutes. An ether-gauging curve was derived from each peak area for each 1 µl of n-Hexane fraction measured by GC. The conditions for GC were as follows. He was used as carrier gas at a flow rate of 40 ml/min. Detector temperature was at 200°C. The column used was CBP-1 (0.32 mm inner diameter and 30 m in length) with analysis temperature at 40°C.

Statistical analysis: All the values were presented as mean ± SEM (standard error of the mean). Statistical differences among groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison method. Differences were considered statistically significant at p < 0.05(*) and p < 0.01(**).

RESULTS

Survival rate: In 3 dogs receiving the I-II-III experiments in turn, all died in experiment II due to ventricular fibrillation (VF) or standstill. Therefore, experiment III was not done in these dogs. In 3 dogs receiving the II-III-I experiments in turn, all were alive. In 3 dogs receiving the III-I-II experiments in turn, all died in experiment II due to VF or standstill. As a result, the number of the dogs survived were 9 of 9 dogs in group I (100%), 3 of 9 dogs in group II (33.3%), and 6 of 6 dogs in group III (100%), respectively.

Incidence of arrhythmia: Table 2 showed the incidence of arrhythmia during each experiment. In group II, 6 dogs died due to cardiac arrest with VF or standstill after remarkable bradycardia (ventricular rhythm) during cooling. Serious ventricular
tachycardia (VT) occurred frequently in 3 of 6 dogs in group III. Single ventricular premature contraction (VPC) occurred in 5 of 9 dogs in group I, in 2 of 9 dogs in group II, and 1 of 6 dogs in group III. VPC was not recorded in 4 of 9 dogs in group I, 1 of 9 dogs in group II, and 2 of 6 dogs in group III, respectively.

**Blood ether concentration**: Blood ether concentrations of dogs in groups I, II and III were proportional to inhaled ether volumes (Fig. 2). In all groups, blood ether concentrations increased according to the increased inhaled volume and reached the peak at 25°C of ET during cooling, because ether inhalation was stopped upon completion of the third stage at ET 30°C to 25°C. The blood ether concentration of the dog in group I was 65 mg/dl at the end of the first ether stage, 105 mg/dl at the end of the second ether stage, 166 mg/dl at ET of 30°C, 168 mg/dl at ET of 25°C, and 153 mg/dl at ET of 20°C during cooling, respectively.

**Hemodynamic findings**: 

**Heart rate (HR)**

HR of all groups increased rapidly after induction of ether anesthesia. HR of groups I and III decreased slowly during cooling, and recovered rapidly during rewarming. In contrast, HR of group II decreased rapidly during cooling and increased slowly during rewarming. The differences in HR between group I or III and group II were statistically significant during cooling and rewarming (p < 0.01 or p < 0.05) (Fig. 3).

**Cardiac output (CO)**

CO levels increased after induction of ether anesthesia, then decreased during cooling, and re-increased during rewarming with the highest value in group I and the lowest in group II. The difference in CO between group I and group II was statistically significant at 30°C and 25°C during cooling (p < 0.05) (Fig. 4).

**Aortic mean pressure (AOMP)**

AOMP in group II decreased remarkably after induction of ether anesthesia, during cooling and rewarming. AOMP of group I showed slight fluctuation and was maintained higher levels throughout. In contrast, AOMP in group III showed a rapid decrease during cooling but a rapid increase after the beginning of rewarming. The difference in AOMP between group I or III and group
Fig. 4. Changes in cardiac output (CO) of three groups during hypothermia.
   I : Group I, II : Group II, III : Group III

Fig. 5. Changes in aortic mean pressure (AOMP) of three groups during hypothermia.
   I : Group I, II : Group II, III : Group III

Fig. 6. Changes in pulmonary artery mean pressure (PAMP) of three groups during hypothermia.
   I : Group I, II : Group II, III : Group III

II was statistically significant during cooling and rewarming (p < 0.01 or p < 0.05). At ET of 20°C, AOMP in group I was significantly higher than those in group II and III (p < 0.01) (Fig. 5).

Pulmonary arterial mean pressure (PAMP)

PAMP increased after ether anesthesia, then decreased during cooling and re-increased after rewarming with the highest value in group II and the lowest in group III. However, the difference in PAMP between groups was not statistically significant, except for those between group II and III group at ET of 25°C during cooling and at 30°C during rewarming (p < 0.05) (Fig. 6).

Central venous pressure (CVP)

CVP increased during hypothermia (from ET of 30°C during cooling to 35°C during rewarming), with the highest value in group II and the lowest in group III. The differences in CVP between group II and groups I or III were statistically significant except at ET of 20°C (p < 0.01 or p < 0.05) (Fig. 7).

Pulmonary capillary wedge pressure (PCWP)

Changes in PCWP during hypothermia was similar to those of CVP, except at ET of
Fig. 8 Changes in pulmonary capillary wedge pressure (PCWP) of three groups during hypothermia. I : Group I, II : Group II, III : Group III

20°C, and PCWP of group II was the highest and that of group III was lowest. The differences in PCWP between group II and group I or III group were statistically significant (p < 0.01 or p < 0.05) (Fig. 8).

Blood gas findings:

Blood pH and base excess (BE)

During hypothermia (from the beginning of cooling to ET at 35°C during rewarming), pH and BE declined in proportion to the depth of ether anesthesia. The differences in pH or BE between groups were statistically significant (p < 0.01 or p < 0.05) (Fig. 9 and 10).

PaCO₂

PaCO₂ of all groups showed little fluctuation because ventilation was controlled using a respirator during the experiment (Fig. 11).

PaO₂

PaO₂ decreased after the beginning of anesthesia, but during hypothermia, PaO₂ increased in proportion to the decrease in ET and decreased again during rewarming, because O₂ consumption decreased during hypothermia (Fig. 12).

Urine volume:
Total urine excretion during hypothermia was well maintained in groups I and III, whereas it was low in group II. The differences between groups I and III and group II were statistically significant ($p<0.01$ and $p<0.05$) (Fig.13).

**DISCUSSION**

**Arrhythmia frequency:**

During hypothermia, attacks of Vf were the most serious danger in the cooling period, especially below 28°C of ET1, 21, 22. Therefore, deep ether anesthesia was hazily preferred to light ether anesthesia for avoiding the attacks of Vf. In this experiment, however, 6 of 9 dogs died of severe arrhythmia (Vf or ventricular standstill) in the deep ether anesthesia (group II), and serious VT occurred in 3 of 6 dogs of the light ether anesthesia (group III). In contrast, no VPC occurred in 4 of 9 dogs and sporadic VPC in the remaining 5 dogs in middle ether anesthesia (group I). Accordingly, it appeared that middle ether anesthesia was the safest for surface-induced hypothermia in the dog.

According to Sano21, the frequency of arrhythmia in deep ether anesthesia was lower than that in neuroleptanalgesia or in thiopental sodium anesthesia. However, Hosoi et al.7 reported the early appearance of arrhythmia in the complication group against no arrhythmia in the no complication group in human clinical cases using simple deep hypothermia with deep ether anesthesia. It was suggested that their complication group corresponded to group II or III of our experiment.

**Hemodynamics during hypothermia:**

According to Wakusawa et al.16, 22, low blood pressure and bradycardia were important factors for simple deep hypothermia, contributing to hypoxemia of tissue and brain injury after hypothermia.

In this experiment, during hypothermia (from ET of 30°C of the cooling period to 30°C of the rewarming period), hemodynamic findings of groups I and III were significantly better than those in group II, especially in HR, CO and AOMP. Although AOMP was depressed in the order of groups III > I > II before ET at 30°C during cooling, AOMP in group III drastically decreased when ET was lower than 30°C. During
hypothermia under ET of 30 °C, the hemodynamics seemed the most unstable in this group. AOMP of group I was significantly higher than that of groups II and III at ET of 20°C (p < 0.01). From these results, it seemed that the hemodynamics of middle ether anesthesia was better than that of light and deep ether anesthesia during hypothermia.

**Urine volume:**

Urine volume is usually a good indicator of the peripheral blood circulation under normal temperature. In this experiment, total urine volume during the procedure was greater in the order of groups III > I > II and was in proportion to the depth of ether anesthesia during hypothermia. The differences between group II and group III or I were statistically significant (p < 0.01 and p < 0.05). AOMP, a good indicator of the central blood circulation, was better in group I than in group III during severe hypothermia under ET of 30°C. However, the urine volume of all groups markedly decreased during severe hypothermia. Therefore, urine volume mainly reflected the hemodynamics before cooling and after 30 °C of rewarming, but did not in hypothermia under ET of 30°C.

**Blood gas:**

Acidosis was reported in hypothermia, and was thought to be a common sign of this condition. In this experiment, it was also an important sign of the depth of ether anesthesia. Blood pH of the three groups showed no fluctuations until the end of the first stage of ether anesthesia. However, the deep ether anesthesia group showed a tendency to decrease to the end of the second stage of ether anesthesia (about pH 7.23). During hypothermia (from ET at 30°C during cooling to 35°C during rewarming), blood pH of light ether anesthesia was about 7.35 and was never below pH 7.30. Blood pH of the middle ether anesthesia group was about 7.25, not lower than 7.20. In the deep ether anesthesia group, blood pH lowered to about 7.10 and was significantly lower than those in the light or middle groups (p < 0.01 or p < 0.05).

Blood BE showed the similar change as that of blood pH. Although blood BE showed no difference among the three groups at the end of the first stage of ether anesthesia, blood BE of the deep ether group dropped significantly to about −10 compared to the value of −4.9 of the light ether group at the end of the second stage of ether anesthesia. During hypothermia, BE of the light ether group was about −7 and was never below −10. Blood BE of the middle ether group was about −12 and was never below −15. In the deep ether group, BE dropped to about −18 and was significantly lower than those of other two groups (p < 0.01 or p < 0.05).

As an indicator of the depth of ether anesthesia, Guedel’s classification has originally been used. During hypothermia, however, it is difficult to determine the depth of ether anesthesia by observing the pupil size of the eye, respiratory manner and nerve reflexes because the dog was covered with a vinyl sheet and immersed in ice water. This experiment suggested that blood pH and BE were especially reliable indicators of ether anesthesia, as arrhythmia and AOMP for the hemodynamics during hypothermia.

**Blood ether concentration:**

The mean blood ether concentration of the middle ether anesthesia group at ET of 20 °C was 153 mg/dl. Miyazaki et al. reported
the value at ET of 20°C in human hypothermia as 285.7 mg/dl, which was near to that of group II in this experiment. The value of 180 mg/dl reported by Wakusawa et al.\(^2\) was near to that of group I in this experiment. Moreover, this value in the dog reported by Hosoi et al.\(^6,\)\(^7\) was 200–250 mg/dl. Because these values in blood ether concentration were measured by old complex procedures, the difference of these values was thought to be due to the measurement technique used.

According to Coleman’s study\(^2\) using new methods, the blood ether concentration of plane I in surgical stage II was 80–110 mg/dl, and that in stage III was 140–180 mg/dl at room temperature. In surface-induced hypothermia, the depth of ether anesthesia during cooling is the most important for prevention of the cold stress, especially at the beginning of cooling. The blood ether concentration (105 mg/dl) of our group I at the beginning of cooling coincided with that (80–110 mg/dl) in plane I of surgical stage III of Coleman’s study, and the value of 153 mg/dl of group I at ET of 20°C coincided with that (140–180 mg/dl) in surgical stage IV of his study at room temperature.

CONCLUSION

1) Concerning hemodynamics during hypothermia, ether anesthesia in groups I and III was significantly better than that in group II. Especially, AOMP of group I was significantly superior to that of group III at ET of 20°C. The incidence of severe arrhythmia was higher in groups II and III. Therefore, ether anesthesia used in group I was demonstrated to be the best for surface-induced hypothermia in the dog.

2) Blood pH and BE as well as arrhythmia and AOMP were excellent indicators for evaluating the depth of ether anesthesia.

3) The optimal mean blood ether concentration determined during hypothermia in the dog was 153 mg/dl at ET of 20°C.

REFERENCES


和文要約

エーテル麻酔深度が低体温麻酔法の血行動態と血液ガスに及ぼす影響をビーグル成犬を用いて調べた。エーテル麻酔深度により3群に分けた；すなわちI（中麻酔）群、II（深麻酔）群、III（浅麻酔）群である。重篤な不整脈がII群とIII群で認められ、II群の6頭（66.7％）は心室細動と心室停止で死亡した。低体温麻酔中の血行動態は、I群とIII群がII群よりも有意に良好であった。また、I群の平均動脈圧（AOMP）はII群よりも良好であり、特に食道温20℃では有意な差が認められた（p < 0.01）。したがって、I群のエーテル麻酔深度が最も良い成績を示した。また、I群の血中エーテル濃度は、食道温20℃で153 mg/dlであった。さらに、低体温麻酔中の血液pHとBEは血中エーテル濃度と良い相関を示したため、血液pHとBEは不整脈とAOMPとともにエーテル麻酔深度の良い指標となることが示唆された。