EFFECT OF CYCLOPROPANE ANESTHESIA ON THE GLUCOSE AND EPINEPHRINE LEVELS OF THE BLOOD * †

W. B. YOUMANS, Ph.D., C. P. WANGEMAN, M.D.,‡ H. E. GRISWOLD, JR., B.A., AND A. I. KARSTENS, B.A.

Portland, Ore.

EXPERIMENTAL work on dogs has demonstrated that cyclopropane anesthesia increases the tendency of epinephrine to produce ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation (1, 2). The increased sensitivity of the automatic tissues of the heart to epinephrine is directly related to the concentration of cyclopropane in the anesthetic mixture (1). Various reports (3) indicate that the administration of epinephrine to patients anesthetized with cyclopropane may produce death from ventricular fibrillation. Cardiac irregularities commonly occur during cyclopropane anesthesia in the absence of the injection of epinephrine (4, 5). In experimental animals the irregularities are more apt to occur if anoxia is a complicating factor (4, 6); however, Orth, Lee, and Meek (7) have recently reported the production of ventricular tachycardia and fibrillation during administration by artificial respiration of a mixture containing 70 per cent cyclopropane and 30 per cent oxygen. Ventricular fibrillation occurred in 4 of 12 animals receiving this mixture even though the oxyhemoglobin did not fall below 90 per cent. The mechanism of production of cardiac irregularities by anoxia under moderate concentrations of cyclopropane or by high concentrations of cyclopropane in the absence of anoxia has not been explained. The liberation of epinephrine from the adrenal medullae could be a factor in either case. In view of these facts it is essential to know if liberation of epinephrine regularly accompanies any level of uncomplicated cyclopropane anesthesia, or if significant quantities of epinephrine may be liberated as a result of certain complications which may be encountered during administration of cyclopropane.

Barman (8) attempted by means of transfusion experiments to determine if cyclopropane causes an increase in the secretion of epinephrine. He anastomosed the suprarenal vein of a donor dog to the jugular vein of a recipient dog and sensitized the latter to epinephrine by atropine and cocaine. The donor dog was then given concentrations of

* From the Department of Physiology, University of Oregon Medical School, Portland, Oregon.

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‡ Presently located at Barnes General Hospital, Vancouver, Washington.

15 per cent to 75 per cent cyclopropane in oxygen for as long as thirty minutes. The results failed to indicate any adrenal discharge or change in basal secretion of epinephrine in the donor dog.

In the present study we have determined the effect of injection of epinephrine at physiological rates on the blood sugar level in dogs under cyclopropane anesthesia. Having found that the hyperglycemic response to epinephrine is unimpaired by cyclopropane anesthesia, we have determined the blood sugar level throughout the stages and planes of anesthesia with cyclopropane in normal animals and in animals with the adrenal medullae inactivated. On the basis of the results obtained it is possible to draw some conclusions concerning the effect of cyclopropane anesthesia on adrenal medullary activity.

METHODS

Cyclopropane in oxygen was given to dogs by the closed to-and-fro carbon dioxide absorption technic. No premedication was used. Adequate oxygenation was insured by the use of an intratracheal catheter when necessary, and the animal was respired by rhythmic pressure on the bag when in the lower planes of anesthesia. In some cases the anesthesia was accidentally complicated by obstruction of the airway resulting from excessive secretions of the unpremedicated animals. In other cases asphyxia was produced intentionally.

Blood samples for the sugar determinations were taken from the femoral artery before the beginning of the anesthesia and at intervals up to forty minutes of surgical anesthesia. The blood sugar was estimated on an iron filtrate using the Shaffer-Somogyi copper reagent.

Injections of epinephrine were given intravenously by a constant injection apparatus. Solutions of epinephrine, 1 part in 250,000, were accurately prepared in saline buffered at a pH of 5 and were used a few minutes after preparation. The solution was given at a rate of 0.1 cc. per kilogram per minute.

RESULTS

I. *Effect of Cyclopropane Anesthesia on the Hyperglycemic Response to Epinephrine.*—Eighteen experiments on 8 normal dogs were completed to determine if cyclopropane has an effect upon the action of epinephrine in increasing the blood sugar level. Epinephrine was injected at the standard rate of 0.0004 mg. per kilogram per minute for a period of ten minutes. Three blood samples were taken as follows: (1) just before the beginning of the injection, (2) at the end of the ten minute injection period, and (3) ten minutes after the cessation of the injection. The injections into the anesthetized animals were begun after forty minutes of anesthesia at which time, as discussed below, the blood sugar was frequently somewhat above the level before the beginning of the anesthesia.

In 16 experiments each of the dogs showed at the end of ten minutes of injection of epinephrine a blood sugar level between 10 and 32 mg. per cent above the pre-injection level. This degree of increase was obtained whether the animal was anesthetized with cyclopropane or was unanesthetized. In 2 other experiments in which the anesthesia was complicated by anoxia the blood sugar rose 57 and 106 mg. per cent above the pre-injection level. The results indicate that cyclopropane does not interfere with the ability of epinephrine to produce a rise in the blood sugar level.

II. *Effect of Cyclopropane Anesthesia on the Blood Sugar Level.*—Waters and Schmidt (9) determined the blood sugar in 21 patients given cyclopropane anesthesia uncomplicated by respiratory obstruction, low oxygen concentration, or technical errors. The blood sugars averaged 96 mg. per cent before the operation, 111 mg. per cent at the end of the operation, and 98 mg. per cent four hours later. The spread was not great except that 1 patient showed a blood sugar of 167 mg. per cent at the end of the operation. Although it is not known to what extent premedication and operative procedures were responsible for changes in blood sugar in these patients, the mildness of the rise indicates that cyclopropane itself has little, if any, effect on the blood sugar level. Results reported by Neff and Stiles (10) indicate that cyclopropane has virtually no effect on the blood sugar level of controlled diabetic patients. Sartori and Rennella (11) studied the fasting blood sugar in 19 dogs before administering cyclopropane and after 40 minutes of anesthesia in the various planes of stage III. Six of their dogs showed no significant change in the blood sugar after forty minutes of anesthesia; 9 showed a mild rise of 6 to 25 mg. per cent, and 4 showed a rise of 31 to 35 mg. per cent.

We have studied the effect of cyclopropane on the blood sugar level in 10 dogs. In each case a fasting sample was taken before the beginning of anesthetization; another sample was taken shortly following the cessation of struggling, and a third sample was taken after thirty to forty minutes of anesthesia in stage III or below. The average fasting blood sugar was 74 mg. per cent. The average blood sugar at the end of the struggling stage was 75 mg. per cent, and the variation from the preanesthetic level was from — 3 to + 6 mg. per cent. Since there is no significant increase in blood sugar following the struggling stage of cyclopropane anesthesia it seems justified to conclude either that no significant quantities of epinephrine are liberated during this stage or, if so, other mechanisms are simultaneously acting which tend to promote a fall in the blood sugar level and perfectly counteract the action of epinephrine. If the latter interpretation were the correct one a fall in blood sugar should be expected to occur following induction with cyclopropane in animals having the adrenal medullae inactivated. However, in 7 experiments with 3 dogs having the adrenal medullae denervated or demedullated cyclopropane anesthesia did not cause a

fall in the blood sugar level. The results indicate that the struggling stage of cyclopropane anesthesia is not accompanied by sufficient liberation of epinephrine to cause a rise in blood sugar even though liberation of epinephrine at a rate of less than 0.0004 mg. per kilogram per minute should be effective in causing a detectable increase.

Of 8 dogs which were maintained at stage III anesthesia with cyclopropane for thirty to forty minutes: 3 dogs showed a change in the blood sugar level of between —1 and + 3 mg. per cent; 3 showed a rise in blood sugar of between 13 and 18 mg. per cent, and 2 showed an increase in blood sugar of 31 and 37 mg. per cent. These results confirm those of Sartori and Rennella (11) described above, and they indicate that a rise in the blood sugar level is not an essential feature of prolonged cyclopropane anesthesia in stage III when respiratory exchange is adequate. It may be inferred, therefore, that cyclopropane anesthesia may be maintained at stage III in about 30 per cent of the experiments without sufficient activation of the adrenal medullae to cause a change in the blood sugar level. We have not at present determined the cause of the rise in blood sugar when it does occur. It cannot be assumed that it is caused by epinephrine.

In 6 experiments in which the animals were taken to stage IV for a short period of time and ventilated artificially the blood sugar showed an increase to between 20 and 86 mg. per cent above the level before anesthetization. This occurred even though an attempt was made to maintain adequate ventilation of the alveoli by artificial respiration.

III. *Effect of Respiratory Complications on the Blood Sugar Level under Cyclopropane Anesthesia.*—Since, under favorable conditions, cyclopropane anesthesia may be induced and maintained in the surgical stage without any change in the blood sugar level occurring, a severe rise in the blood sugar under cyclopropane is most likely attributable to complications. The following protocols will serve to illustrate that a rise in the blood sugar level under cyclopropane may be induced by asphyxia.

Dog C. S. No. 6. 12/26/41. *Inadequate respiration in stage* III_{3-4}. The fasting blood sugar at 9:25 a.m. was 81 mg. per cent. Induction was begun at 9:32 and completed without complications. The dog was maintained at stage III until 10:12 and at planes 3 to 4 part of this time. There were periods of convulsive movements of the hind limbs. The blood sugar at 10:12 was 186 mg. per cent. Epinephrine was injected at a rate of 0.0004 mg. per kilogram per minute for ten minutes. At the end of the period of injection the blood sugar was 222 mg. per cent.

Dog S. A. No. 1. 3/16/42. *Respiratory arrest without artificial respiration.* The fasting blood sugar at 3:50 p.m. was 76 mg. per cent. Cyclopropane anesthesia was begun at 3:55. After cessation of struggling at 4:00 the blood sugar was 73 mg. per cent. The dog was kept in stage III, and at 4:10 the blood sugar was 78 mg. per cent. The anesthesia was deepened to respiratory arrest at 4:15

and was maintained at this level for six minutes. At 4:19 the blood sugar was 85 mg. per cent, and at 4:21 it was 107 mg. per cent.

SUMMARY AND CONCLUSIONS

Cyclopropane anesthesia in dogs does not interfere with the production of a significant rise in the blood sugar level by intravenous injection of epinephrine at a rate of 0.0004 mg. per kilogram per minute.

A mild rise in blood sugar of less than 20 mg. per cent commonly occurs under cyclopropane anesthesia when there are no obvious complications. The cause of the rise has not been determined.

Cyclopropane anesthesia was induced and maintained in the second and third planes of stage III in about 30 per cent of the experiments without a change in the blood sugar level occurring at any stage. It may be inferred that activation of the adrenal medullae is not an essential feature of uncomplicated cyclopropane anesthesia.

A rapid rise in the blood sugar level may be induced in dogs under cyclopropane anesthesia by a period of asphyxia. However, the magnitude of the rise is quite variable. The role of the sympatho-adrenal system in the production of the hyperglycemia is being studied.

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