EFFECTS OF GENERAL ANESTHETICS ON TISSUE OXYGEN TENSION IN MAN: SKIN

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CELLULAR function and respiration are dependent upon the presence of oxygen in amounts adequate to maintain normal aerobic metabolism. The amount of oxygen present in tissue is a function of (1) the rate at which arterial blood is delivered to the tissue; (2) the amount of oxygen present in the arterial blood; (3) the rate at which oxygen is being consumed by tissue, and (4) the diffusion coefficient of oxygen in tissue fluids. With the possible exception of the fourth factor, each of the other determinants of the amount of oxygen in tissue is, in turn, related to a large number of physiological variables. Some of the more important of these are: oxygen concentration in inspired air, alveolar ventilation, oxygen carrying capacity of the blood, cardiac output, blood pressure, the state of the peripheral vasculature (whether vasoconstricted or vasodilated), and the presence or absence of calorigenic substances such as anesthetics, epinephrine, and thyroxine. Inasmuch as general anesthetics have profound effects on many of these variables, it is impossible to estimate what effect, if any, anesthetics have under clinical conditions on the amount of oxygen in and available to tissues. Studies of cardiac output and pulmonary ventilation provide invaluable data, but in themselves they reveal little in answer to the question: how much oxygen is there in tissues during abnormal situations such as anesthesia? Even measurements of tissue blood flow in terms of cubic centimeters of blood per 100 Gm. of tissue per minute do not invariably reflect the state of tissue oxygenation.[1] A study was accordingly instituted to obtain measurements of tissue oxygen concentration in terms of tissue oxygen tension. The present report deals with three commonly used general anesthetic agents and their effects on skin oxygen tension. The effects of spinal and epidural anesthesia on skin oxygen tension have been reported elsewhere.[1] It should be emphasized that the results deal only with oxygen tension. They do not indicate whether the tissue can utilize the oxygen that is present. Nor do they indicate whether the amount of oxygen present, if it can be utilized, is adequate to maintain normal cellular function and respiration under abnormal conditions.

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METHODS

Polarography. Polarographic methods were used. These depend upon the fact that when a fixed low voltage is applied to a circuit containing a platinum electrode inserted into a liquid or a tissue, the oxygen about the electrode is reduced and the resulting current is proportional to the amount of oxygen present. Polarography has certain inherent and definite limitations.[2, 3] Not the least of these is inability to calibrate results in terms of millimeters of mercury oxygen tension.[4] Nevertheless, valuable information can be obtained by polarography which presently cannot be obtained in any other manner. The technique used, described in detail elsewhere,[1] is based upon the open-tipped electrode method of Montgomery and Horwitz.[5] The electrodes were individually made and tested by ourselves. The exposed portion of the electrodes, made under the microscope, had surface areas of approximately 0.043 mm.[2] in order to avoid cellular and vascular trauma insofar as possible. Following insertion of the platinum electrode into the skin, an indifferent electrode was applied nearby and a known voltage introduced to complete the circuit. The resulting current was recorded using a Rubicon spot galvanometer. The known voltage applied was gradually increased from 0.2 to 0.8 volt in increments of 0.1 volt in order to assure that the resulting amperage fell within the plateau portion of the established oxygen reduction curve.[6] The mid-portion of our plateau was 0.6 volt as reported by others.[7] To assure equilibrium

within the circuit, all galvanometric readings were taken 20 seconds after the voltage had been applied. To allow recovery of the electrode, readings were taken at intervals of 2 minutes. Electrode responsiveness and decay were checked as previously described.[1] In all cases the indifferent electrodes consisted of saline-silver chloride bridges. The results are given in terms of glavanometric units, the sensitivity of the galvanometer remaining unchanged during each experiment. No attempt has been made to interpret amperage (as expressed by galvanometric units) in terms of oxygen tension (as expressed by millimeters of mercury). Nevertheless, an increase or decrease in galvanometric units corresponds to a proportionate increase or decrease in oxygen tension.

Clinical. In the majority of cases the platinum electrode was placed in the skin of the flexor surface of the forearm. In some, the skin of the lateral aspect of the calf was employed. Results were identical at the two sites. The electrode was inserted into the skin through a small intracutaneous puncture made with a 25 gauge needle. Care was taken to avoid bleeding, subcutaneous insertion, "tenting" or other distortion of the skin, or motion of the electrode. If any of these occurred, the case was eliminated from further study. At least two base-line readings were obtained, following which anesthesia was induced and repeated readings taken every 2 minutes for the next 50 minutes or longer. During this time operation was started.

Patients studied were 19 to 77 years old and were unselected as to operation except that those receiving thiopental-nitrous oxide-oxygen anesthesia had operations requiring no muscle relaxation. Only those patients were studied who had neither clinically apparent peripheral vascular disease nor metabolic or endocrine diseases. Premedication consisted of sodium pentobarbital, 100 mg./70 kg., and atropine, 0.4 mg./70 kg., intramuscularly, 45–60 minutes prior to anesthesia. Anesthesia was administered by experienced anesthesiologists in order to reduce the incidence of extraneous factors such as coughing, breath-holding, vomiting, laryngospasm, or pharyngeal obstruction. If such did occur, the patient was eliminated from the study inasmuch as the purpose of the investigation was to study skin oxygen tensions during uncomplicated anesthesia. No other anesthetic agents, barbiturates, muscle relaxants, or vasopressors were administered. Respirations were manually assisted or controlled when necessary in order to assure adequate ventilation. The tendency was to hyperventilate patients during cyclopropane anesthesia. Carbon dioxide absorption was employed throughout. Care was taken to assure a gas-tight fit between the patient's face and the anesthesia mask. Arterial blood pressure was determined by sphygmomanometry. Studies did not extend beyond the time when anesthesia was discontinued.

Six patients were studied during uncomplicated nitrous oxide-oxygen-ether anesthesia. This was administered using a Heidbrink anesthesia machine with a 5-liter breathing bag and with a no. 8 ether vaporizer on the inspiratory side. Induction was performed using flows of 4 liters of nitrous oxide and one liter of oxygen for 2 minutes, following which the ether concentration was increased in a step-wise fashion (approximately one-half number every 6 breaths) until the vaporizer was fully opened (about 7–8 minutes after start of induction). When the patient had entered stage III, as judged by clinical signs, nitrous oxide was turned off over a period of 2–4 minutes, oxygen flow being maintained at one liter per minute for the remainder of the study. The amount of inspired air passing through the ether vaporizer was gradually decreased following induction in order to maintain a constant plane of surgical anesthesia (usually plane 2 by clinical signs).

Six patients were studied during uncomplicated cyclopropane anesthesia. Induction was accomplished by having the patient take one breath from a rebreathing bag one-third filled with oxygen, immediately after which flows of 500 cc. of cyclopropane and 1,000 cc. of oxygen per minute were started. These were continued for approximately 3 minutes after the excitement stage had been passed, the cyclopropane then being decreased over a period of 4–6 minutes to 200–300 cc. per minute, the oxygen being maintained at one liter per minute. Additional cyclopropane was added in measured amounts as indicated in order to maintain adequate levels of anesthesia. This

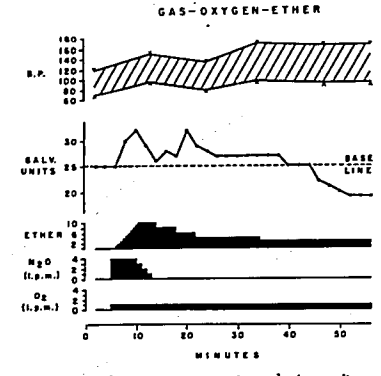

FIG. 1. Skin oxygen tension during nitrous oxide-oxygen-ether anesthesia. *Ordinate* (from above down): blood pressure in mm. of mercury (v systolic, ^ diastolic pressures); skin oxygen tension in galvanometric units; setting on no. 8 Heidbrink ether dial on inspiratory side of circuit; nitrous oxide in liters per minute; oxygen in liters per minute. *Abscissa:* time in minutes.

usually required approximately 25 per cent cyclopropane.

Seven patients were studied during uncomplicated thiopental-nitrous oxide-oxygen anesthesia. Induction consisted of a 2 cc. intravenous test dose of 2.5 per cent thiopental, followed by 5 cc. doses until the lid reflex was obtunded, at which time 3.5 liters of nitrous oxide and one liter of oxygen per minute were started. The concentration of gases was kept constant throughout the remainder of the study, supplemental thiopental being administered when indicated in dosages just adequate to prevent motion by the patient in response to operative stimuli.

Three normal volunteers were studied during the administration of helium and oxygen to differentiate between the effects of breathing anesthetic gases in the presence of high oxygen concentrations and the effects of breathing inert gases in the presence of high oxygen concentrations. Although helium has a different density, viscosity, and solubility coefficient than the anesthetic gases studied, after a steady state has been achieved the tension of oxygen in arterial blood will be the same as it is when oxygen is administered with anesthetic gases in the same manner. The helium-oxygen mixture was administered to the volunteers in exactly the same fashion as if cyclopropane-oxygen were being used to induce and maintain anesthesia.

RESULTS

Results did not vary according to age, sex, or type of operation. No change was observed which could be related to the time at which the surgical incision was made. Similarly, no change in skin oxygen tension could be detected (after a steady state had been reached) which could be ascribed to the depth of anesthesia, although no attempt was made to examine this point further by the use of extreme depth. The results were influenced by the anesthetic agent.

Nitrous Oxide-Oxygen-Ether. All patients, with only minor variations, showed essentially the same pattern of changes in skin oxygen tension during nitrous oxide-oxygen-ether anesthesia. A characteristic response is shown in figure 1. (When examining the figures the important factor to be noted is the percentile

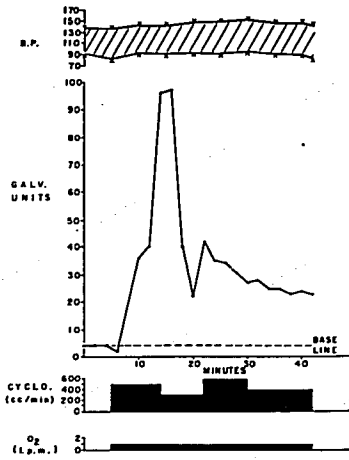

FIG. 2. Skin oxygen tension during cyclopropane anesthesia. See legend accompanying figure 1. Cyclopropane flow in cubic centimeters per minute, oxygen in liters per minute.

change from control levels in galvanometric readings. Because different base-lines were present in individual patients, neither the absolute reading in galvanometric units nor the number of units change is as significant as the percentile change.) Typically there was an initial increase of 50–75 per cent in skin oxygen tension during induction, although in 2 cases induction was associated with a prompt decrease below control levels. Following induction and as a steady state of surgical anesthesia was achieved, oxygen tensions leveled off either slightly above or slightly below control levels. In 2 cases these levels were 25 per cent above, in 2 cases 30 and 50 per cent below, and in 2 cases so close to the baseline that consecutive readings were slightly above or below control levels.

Cyclopropane. Skin oxygen tensions during cyclopropane anesthesia invariably showed a marked rise during induction followed by an invariable decrease in the direction of, but not to, control levels (fig. 2). The initial rise in oxygen tension was more pronounced with cyclopropane than with nitrous oxide-oxygen-ether anesthesia, varying from a three-fold to as high as a twenty-fold increase. These increases were maintained at a plateau for 2–10 minutes and then were followed by a decrease

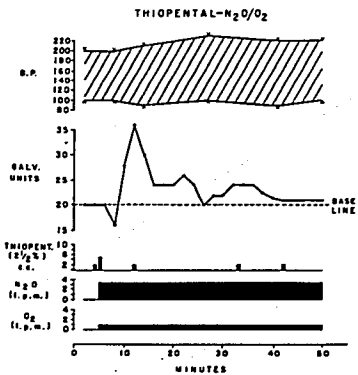

FIG. 3. Skin oxygen tension during thiopental-nitrous oxide-oxygen anesthesia. See legend, figure 1. Thiopental (2.5 per cent) dosage in cubic centimeters. Nitrous oxide and oxygen flows in liters per minute.

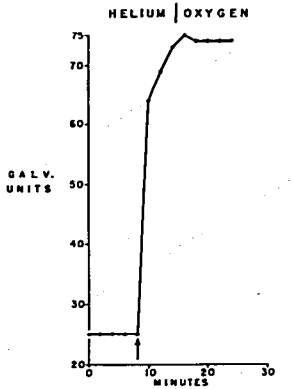

FIG. 4. Skin oxygen tension during administration of helium and oxygen so as to simulate cyclopropane and oxygen administration.

in tension to a new lower level. The oxygen tension levels during maintenance of cyclopropane anesthesia were 2 to 7 times greater than control levels.

Thiopental-Nitrous Oxide-Oxygen. This type of anesthesia was associated in 2 patients with a transient two-fold elevation in oxygen tension during induction (fig. 3). In 2 other patients there was an initial two-fold decrease while in 3 patients there was essentially no change during induction. During maintenance of anesthesia, skin oxygen tensions showed a tendency to return towards control values. In 3 patients, tensions were essentially the same as control levels, in 2 patients they were 20 and 30 per cent below, and in 2 patients they were 5, 15, and 60 per cent above.

Helium-Oxygen. In all 3 cases studied, administration of helium and oxygen in exactly the same manner as the administration of cyclopropane and oxygen resulted in a prompt rise in skin oxygen tension which was sustained as long as the study continued (fig. 4). Plateau readings were 3 to 7 times greater than control readings.

DISCUSSION

If the general anesthetic agents studied had no effect on skin oxygen tension, it would be expected that skin oxygen tension during their

administration would be related solely to concurrent changes in the amount of oxygen present in the inspired air. For example, hypothetical general anesthetic agent "A" produces surgical levels of anesthesia in concentrations of 50 volumes per cent "A" in 50 volumes per cent oxygen. If "A" has no direct effect on the various determinants of tissue oxygen tension mentioned above, then during the clinical use of "A" in a semiclosed system, skin oxygen tension should be the same as if an inert, nonanesthetic gas such as helium or nitrogen were administered with the same flow rates in a semiclosed system with 50 per cent oxygen. When studying effects of anesthetic agents on skin oxygen tension, results must be interpreted in terms of the concentration of oxygen with which the anesthetics are administered.

The technique employed in the present study to administer thiopental-nitrous oxide anesthesia results, during maintenance of anesthesia, in concentrations of oxygen in the inspired air which are approximately the same as those found in room air. When thiopental-nitrous oxide was administered in this fashion, skin oxygen tensions showed essentially no difference compared to control levels obtained during breathing of room air. Consequently, the present results indicate that during maintenance of anesthesia, thiopental-nitrous oxide anesthesia has no significant effect on skin oxygen tension.

During maintenance of cyclopropane anesthesia with approximately 25 per cent cyclopropane in the inspired air, skin oxygen tension showed a 2- to 7-fold increase. During administration of 25 per cent helium in inspired air, there were essentially comparable increases in skin oxygen tension. For example, there was a 5-fold increase (from 5 to 25 galvanometric units) in skin oxygen tension during administration of cyclopropane to the patient illustrated in figure 2. This is not significantly different from the 3-fold increase (from 25 to 75 galvanometric units) illustrated in figure 4 when helium-oxygen was administered. In all cases, cyclopropane anesthesia was accompanied by changes in skin oxygen tension which could be ascribed to the fact that the cyclopropane was administered with high oxygen concentrations. It should be pointed out that the observed changes in skin oxygen tension of 2- to 7-fold increases are physiologic in view of the fact that normal resting skin oxygen tension varies from 5 to 30 mm. of mercury when the subject is breathing room air.[5]

During maintenance of ether anesthesia, on the other hand, the results were somewhat different. When nitrous oxide-oxygen-ether anesthesia is administered as in the present series, it can be calculated that the concentration of oxygen in the inspired air averages 75 volumes per cent or more, the remainder being ether (4–7 volumes per cent), nitrous oxide, and nitrogen.[8] Such high concentrations of oxygen were achieved in the patients studied because the flow of oxygen into the semiclosed system was maintained at a constant one liter per minute after the nitrous oxide had been turned off. This flow of oxygen in such a system results in the gradual washout both of nitrous oxide and the nitrogen which was still present following induction. After 20 minutes of such oxygen flows, the percentage oxygen in the inspired air would be 75 per cent or above. If ether had no effect on skin oxygen tensions, it would then be anticipated that skin oxygen tensions would be comparable to those found following inhalation of 75 per cent oxygen in 25 per cent helium (or any other pharmacologically inert gas). Comparison of figures 3 and 4 indicates that such did not occur. Instead, skin oxygen tension during ether anesthesia in the presence of high oxygen concentrations was essentially no different than it was during inhalation of room air. Sometimes it was slightly above control levels, sometimes slightly below, and sometimes it was the same, but there was no significant difference. Accordingly, maintenance of surgical anesthesia with ether was found to be associated in the present series with skin oxygen tensions below those anticipated in view of the high oxygen concentrations administered with the ether.

It is impossible to state, on the basis of the present investigation, why ether anesthesia is associated with decreases in skin oxygen tension. Tissue oxygen tension is dependent upon a number of complex and interrelated phenomena, none of which was studied in the present series. The most plausible hypothesis is that ether is associated with changes in

cutaneous blood flow. The etiology of such changes is unknown, but may be related to concurrent release of epinephrine and norepinephrine, both of which have been shown to cause decreases in skin oxygen tension.[9]

Both cyclopropane anesthesia and nitrous oxide-oxygen-ether anesthesia were accompanied by brief but often marked increases in skin oxygen tension during induction of anesthesia. These did not occur during the induction of thiopental-nitrous oxide anesthesia. Again, the etiology of these transient increases remains undetermined. In the case of cyclopropane, these increases may have been due to the high concentrations of oxygen to which the patient was exposed during the first few breaths of the induction period, or they may have been due to increases in cutaneous blood flow, or they may have been due to both. The increases in skin oxygen tension during induction of nitrous oxide-oxygen-ether anesthesia cannot be ascribed to high concentrations of oxygen in the inspired air, but probably represent instead changes in skin blood flow. With both cyclopropane and ether, the initial elevation of skin oxygen tension is replaced by a lower level following completion of induction, in the case of ether the new level being near base-line levels while with cyclopropane the new levels are considerably above base-line readings.

It should be mentioned that no conclusions can be drawn from the present results regarding the effects, if any, of general anesthetics on oxygen tensions in physiologically more important tissues such as the myocardium, the central nervous system, the kidney, and the liver. Such data are the subject of future investigations.

Summary

Maintenance of surgical planes of uncomplicated ether anesthesia is associated in humans with decreases in skin oxygen tension below those levels which would be anticipated in view of the high oxygen concentration with which the ether was administered. Cyclopropane anesthesia and thiopental-nitrous oxide anesthesia are not associated with any significant changes in skin oxygen tension which cannot be related to the amount of oxygen in the inspired air.

Induction of cyclopropane and ether anesthesia is accompanied by transient but often marked increases in skin oxygen tension.

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