HYPOCAPNIC VASOCONSTRICTION DURING HALOTHANE ANAESTHESIA IN SURGICAL PATIENTS

BY

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SUMMARY

The relation between the carbon dioxide tension of the capillary blood and the state of the blood vessels of the skin has been studied plethysmographically in curarized patients anaesthetized with halothane in oxygen. It was observed that hypocapnia consistently caused constriction of the cutaneous blood vessels. The vasoconstrictive reaction was uninfluenced by hexamethonium bromide but was blocked by phentolamine and by chlorpromazine. It is concluded that carbon dioxide plays an important part in the maintenance of tissue perfusion in anaesthetized patients.

The routine use of a digital plethysmograph as a cardiovascular monitor during surgical operations (Johnstone, 1967) has shown that manual intermittent positive pressure respiration (IPPR) often causes constriction of the cutaneous blood vessels of curarized patients anaesthetized with halothane in oxygen. Pallor of the skin and a fall in its temperature rapidly follow the onset of the vascular reaction. The vasoconstriction is uninfluenced by changes in the depth of halothane anaesthesia, or by the addition of nitrous oxide, pethidine, fentanyl, promethazine, haloperidol or dehydrobenzperidol. The pulsations of the radial arteries are palpably unchanged in the normovolaemic patient, the pulse rate remains relatively constant and the brachial systolic pressure falls slightly when the cutaneous vessels constrict (Johnstone, 1966, unpublished work). In view of the obviously ischaemic state of the skin, possibly indicative of ischaemia in other tissues, it was decided to investigate the reaction in order to determine whether it was due to the reflex effects of surgical trauma, to the mechanical effects of IPPR on the pulmonary circulation, or to hypocapnia. It was decided also to study the part played by the sympathetic nervous system in the reaction: hexamethonium bromide was used to determine the effect of sympathetic blockade at ganglionic level; phentolamine and chlorpromazine were used to assess the reaction of the vasoconstriction to blockade of the alpha-adrenergic receptors.

METHOD

An initial series of five adult females free from respiratory and cardiovascular disease, between the ages of 35 and 45 years, was selected. All were of average height and weight and required abdominal hysterectomies for non-malignant uterine disease. Their cardiovascular and respiratory systems, blood pressures, blood volumes and haemoglobin levels were normal.

Each patient was given haloperidol 5 mg and pethidine 50 mg intramuscularly 1 hour before the induction of anaesthesia. Anaesthesia was induced with an intravenous injection of propanidid 250 mg, diallylnortoxiferine 20 mg and atropine 0.25 mg. Gentle IPPR was applied manually for 3 minutes from a circle system (Boyle Mark 3) fed with oxygen 5 l./min and halothane 3 per cent from a Fluotec Mark 3* vaporizer outside the circuit. A cuffed orotracheal tube was then inserted and a similar dose of halothane in oxygen continued with gentle IPPR and carbon dioxide absorption with soda-lime.

After 5 minutes at the above settings the oxygen flow was reduced to 400 ml/min and the expiratory valve closed. The dial setting of the vaporizer remained at 3 per cent throughout the operation. IPPR was continued at a minute volume of 6 l./min (tidal volume 0.5 l.) as shown

* The dial setting of this newly introduced vaporizer shows accurately the concentration of halothane vapour at oxygen flow rates from 0.25 to 10.00 l./min. Its accuracy of calibration is unaffected by IPPR.
by a Wright respirometer. Overfilling of the circuit was avoided by occasionally opening the expiratory valve. This pattern of IPPR was followed in each patient for 15 minutes, at the end of which the carbon dioxide tension of the capillary blood from a finger was measured by the Astrup technique.

The respiratory minute volume was then increased to 20 l./min (tidal volume 1.00 l.) with a similar dose of halothane (12 ml of vapour/min) and carbon dioxide absorption. The inflationary pressure in the circuit did not exceed 25 cm H₂O. This pattern of IPPR was continued for 15 minutes, after which a second measurement of the carbon dioxide tension of the capillary blood was made. The soda-lime absorber was then excluded from the circuit, and IPPR continued at 20 l./min for a further 20 minutes. The carbon dioxide tension of the capillary blood was again estimated. The carbon dioxide absorber was then brought into circuit and IPPR applied at 6 l./min until the operations were completed. Supplementary doses of the relaxant were not required in any case. Each patient needed neostigmine and atropine to reverse the paralysis at the end of the operation. Blood loss during the operations was negligible and replacement therapy was unnecessary.

The digital plethysmogram of each patient was continuously displayed on an oscilloscope throughout the period of anaesthesia and permanent records were made at appropriate intervals. The systolic blood pressures were measured at 2-minute intervals by the conventional brachial cuff-occlusion technique and either palpation of the radial artery or the disappearance of the pulse wave on the oscilloscope. The minimum cuff pressure which obliterated the plethysmographic pulse-wave was accepted as the systolic pressure when the arm was supported at the same level as the heart.

A second series of eight similar patients was selected in order to study the role of sympathetic activity in the vasoconstrictive reaction to IPPR. Each patient was anaesthetized for hysterectomy in the manner described above and cutaneous vasoconstriction was induced by passive hyperventilation and carbon dioxide absorption. As soon as the vasoconstriction appeared hexamethonium bromide 50 mg was given intravenously to each of three patients. Each of the other five patients was given phentolamine 5 mg intravenously followed 5 minutes later by chlorpromazine 20 mg intravenously because the effect of phentolamine lasted not more than 2 minutes. Hypocapnia was maintained for 15 minutes after the injection of the sympathetic blockers. The carbon dioxide tension then was returned to normal by excluding the soda-lime absorber from the circuit. Digital plethysmograms, systolic blood pressures and the carbon dioxide tensions of the capillary blood were recorded as in the first series.

RESULTS

First series.

Full digital vasodilatation was present in all patients at the end of the first period of IPPR at 6 l./min. At the completion of this period the amplitude of the pulse waves of the five patients ranged from 19 to 25 mm (mean 23 mm); the systolic blood pressures were between 100 and 140 mm Hg (mean 123 mm); and the range of carbon dioxide tensions was 35 to 44 mm Hg (mean 41 mm).

Towards the end of the period of IPPR at 20 l./min with carbon dioxide absorption vasoconstriction occurred in all five patients. The amplitudes of the pulse waves ranged from 2 to 5 mm (mean 3 mm); the systolic blood pressures were between 85 and 125 mm Hg (mean 95 mm); and the range of carbon dioxide tensions was 17 to 23 mm Hg (mean 19 mm).

Full vasodilatation returned slowly in each patient during the period of IPPR at 20 l./min with carbon dioxide retention and was complete in all patients after 20 minutes. At the end of the 20-minute period the amplitudes of the pulse waves of the series ranged from 18 to 27 mm (mean 24 mm); the systolic blood pressures were between 110 and 140 mm Hg (mean 135 mm); and the carbon dioxide tensions were 41 to 52 mm Hg (mean 46 mm). The typical sequence of changes is illustrated in figure 1.

Second series.

Hexamethonium bromide did not influence the vasoconstriction. It lowered the blood pressures and pulse rates of all patients.

Phentolamine decreased the severity of the vasoconstriction in each of the five patients. It
did not notably alter the pulse rate or the systolic blood pressure. The increase in the amplitude of the digital pulse wave appeared within 2 minutes of injection and was followed by a return to the vasoconstricted state about 3 minutes later in each patient.

Chlorpromazine blocked the vasoconstrictive response to hypocapnia in all patients. It was effective within a minute and the effect persisted for at least 15 minutes. Systolic blood pressures were elevated by a mean of 10 mm Hg in three patients after the injections and unchanged in the remainder. Pulse rates were unchanged. The restoration of the carbon dioxide tension to a normal level produced a further increase in the amplitude of the digital pulse wave and moderate increases in the pulse rate and the systolic blood pressure of each patient. The typical response of the hypocapnic vasoconstriction to phentolamine and chlorpromazine is illustrated in figure 2.

DISCUSSION
These results indicate that hypocapnia causes cutaneous vasoconstriction and moderate hypotension in normovolaemic patients anaesthetized with halothane in oxygen. The passive hyperventilation (IPPR) used to produce the hypocapnia plays little or no part in the vasoconstrictive reaction. IPPR with carbon dioxide retention not only fails to induce vasoconstriction but reverses the vasoconstriction induced by hypocapnia.

FIG. 1
Serial digital plethysmograms during halothane anaesthesia; female, 38 years.
A. After 20 minutes anaesthesia: Pco, 41 mm Hg; blood pressure 125 mm Hg systolic.
B. 15 minutes later: Pco, 21 mm Hg; blood pressure 105 mm Hg systolic.
C. 20 minutes later: Pco, 48 mm Hg; blood pressure 135 mm Hg systolic.

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FIG. 2
Serial digital plethysmograms during halothane anaesthesia; female, 41 years.
A. After 20 minutes anaesthesia; Pco, 40 mm Hg; blood pressure 110 mm Hg systolic.
B. 15 minutes later: Pco, 19 mm Hg; blood pressure 95 mm Hg systolic.
C. 2 minutes later, after phentolamine 5 mg i.v.: Pco, 19 mm Hg; blood pressure 95 mm Hg systolic.
D. 3 minutes later: Pco, 18 mm Hg; blood pressure 95 mm Hg systolic.
E. 1 minute later, after chlorpromazine 20 mg i.v.: Pco, 18 mm Hg; blood pressure 100 mm Hg systolic.
F. 30 minutes later: Pco, 45 mm Hg; blood pressure 115 mm Hg systolic.
Pulmonary ventilation was discontinued temporarily when the plethysmograms were recorded.
Lowering of the carbon dioxide tension of the blood is a known cause of cerebral vasoconstriction (Stoddart, 1967). A similar reaction also occurs in dogs lightly anaesthetized with halothane and may be reversed by carbon dioxide (McDowall, Harper and Jacobson, 1963; McDowall, 1967). An ischaemic response to hypocapnia has been reported in the kidneys and intestines (Greishheimer, 1965) and in the myocardia of experimental animals (Vance, McBride and Ledingham, 1967). Hypocapnia induced by artificial respiration in anaesthetized patients lowers their cardiac outputs (Prys-Roberts et al., 1967).

It would appear that the vasoconstrictive reaction to hypocapnia is widespread, is unaffected by anaesthesia, and may impair the perfusion and oxygenation of the tissues. The severity of the vasoconstriction and the tissue ischaemia caused by hypocapnia in surgical patients will be increased by other factors such as hypovolaemia, atherosclerosis, pressor drugs, and the vasoconstrictive reaction to trauma in inadequately anaesthetized patients. A normal or slightly raised carbon dioxide tension may therefore be regarded, with other factors, as essential to the maintenance of tissue perfusion in anaesthetized patients.

The observations made in the second series suggest that the vasoconstrictive response to hypocapnia depends on the alpha-adrenergic receptors and is independent of the sympathetic centre and its efferent connections. This may be another manifestation of the peripheral autonomy of the sympathetic nervous system (Rothlin and Berde, 1949/53). The inability of hexamethonium bromide to prevent the hypocapnic vasoconstriction is not unexpected as the efferent sympathetic pathways to the limb vasculature were already blocked when the hexamethonium was given.

Halothane acts at sympathetic ganglionic level (Raventós, 1961; Price and Price, 1966) to produce a peculiarly selective type of sympathetic blockade. Clinical doses undoubtedly block the vasoconstrictive response to surgical trauma (Johnstone, 1967) and have no appreciable action on the peripheral alpha-adrenergic receptors as assessed by the effectiveness of alpha-adrenergic agonists in anaesthetized patients with normal cardiovascular systems (Johnstone, 1966).

Halothane has comparatively little effect on the reflex sympathetic stimulation of the heart provoked by surgical stimulation of the skin, i.e. the increases in the sinus rate and blood pressure and the occasional appearance of ventricular extrasystoles in lightly anaesthetized patients when the skin is incised. This implies that when the concentration of halothane is only sufficient for light anaesthesia it does not block the function of the afferent sympathetic pathways, the vasomotor centre, or the efferent sympathetic nerves to the heart in man. Its sympathetic blocking action appears to be mainly on the efferent sympathetic connections to the peripheral vasculature. This selectivity may explain the falls in blood pressure and pulse rates which occurred when hexamethonium was given to hypocapnic patients anaesthetized with halothane.

Wiggers (1928) observed that it was necessary to add measured volumes of carbon dioxide to the inspired gases when mechanically controlled respiration was used in experimental animals in order to preserve the efficiency of their cardiovascular systems. Nowadays, with the widespread use of controlled respiration in clinical anaesthesia, it is unfortunate that there is as yet no method of continuously and conveniently estimating the carbon dioxide tension of the blood. Continuous infra-red analysis of the respiratory end-tidal gases has been advised (Burton, 1966) as a suitable substitute in special circumstances.

When it is impossible to measure the carbon dioxide content of either the blood or the end-tidal gases it would seem that the continuous observation of the digital pulse wave will provide a reasonable indication of changes in the carbon dioxide tension of anaesthetized patients, provided the vasoconstrictive reaction to surgical trauma has been blocked by anaesthesia. In the latter circumstances an excessive lowering of the carbon dioxide tension will diminish the amplitude or completely obliterate the digital pulse without seriously affecting the pulsations of the radial arteries. Correction of the carbon dioxide deficit will restore the peripheral vasodilatation. An excess of carbon dioxide in the blood of patients anaesthetized with halothane causes a further increase in the amplitude of the pulse wave, with increases in the pulse rate and blood pressure and ultimately pulse irregularities due to ventricular ectopic beats. These changes are usually recognizable on the digital plethysmo-
gram. Controlled respiration may therefore be used safely during closed-circuit halothane anaesthesia provided the behaviour of the digital pulse wave is continuously observed, the correct dose of halothane is constantly measured from a calibrated vaporizer situated outside the circuit, and the other precautions common to all types of anaesthetic techniques are observed.

ADDENDUM
Since the manuscript was completed further search of the literature has revealed that the hypocapnic shock syndrome caused by excessive artificial respiration was originally observed in anaesthetized animals by Yardell Henderson (1908).

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REFERENCES

Rothlin, E., and Berde, B. (1949/53). The structure and function of the autonomic nervous system. Aerztli. Monatsh., 5, 865. (English translation provided by the Pharmacological Laboratory, Sandoz Ltd., Basle, Switzerland.)
Wiggers, C. J. (1928). The Pressure Pulses in the Cardiovascular System, p. 120. London: Longmans, Green.

VASOCONSTRICTION HYPOCAPNIQUE DURANT L'ANESTHESIE AVEC HALOTHANE CHEZ DES PATIENTS OPERES

SUMMARY
Le rapport entre la pression de gaz carbonique dans le sang capillaire et l'état des vaisseaux sanguins de la peau a été étudié par plethysmographie chez des patients curarisés, anesthésiés avec halothane et oxygène. On a observé que l'hypocapnie provoquait en général une constriction des vaisseaux sanguins cutanés. La réaction vasoconstrictrice n'était pas influencée par le bromure d'hexaméthonium mais bloquée par phentolamine et chlorpromazine. On conclut que le gaz carbonique joue un rôle important dans le maintien de la perfusion des tissus chez les patients anesthésiés.

ZUSAMMENFASSUNG
Bei kurarisierten Patienten, die mit Halothan und Sauerstoff narkotisiert waren, wurde die Beziehung zwischen der Kohlendioxydspannung des Kapillarblutes und dem Zustand der Blutgefäße der Haut verursacht. Die Hypokapnie wurde nicht durch Hexamethoniumbromid beeinflußt, sie wurde jedoch durch Phentolamin und Chlorpromazin gehemmt. Es ergibt sich die Schlußfolgerung, daß bei narkotisierten Patienten das Kohlendioxid bei der Erhaltung der Gewebsdurchblutung eine wichtige Rolle spielt.