OBSERVATIONS ON THE CEREBRAL EFFECTS OF PASSIVE HYPERVENTILATION*

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By 1952 there had developed a strong clinical impression that the use of controlled respiration for abdominal surgery carried out under thiopentone, relaxant, nitrous oxide anaesthesia, resulted in a reduction in the dosage of both relaxant and barbiturate. This led to the suggestion by Gray and Rees (1952) that controlled respiration, quite apart from its use to achieve adequate ventilation, supplemented in some way the anaesthetic and relaxant drugs being used. Dundee (1952) in controlled observations on patients undergoing upper abdominal operations of 2 hours duration confirmed that there was a reduction in dosage of thiopentone necessary but found less evidence of the need for a smaller dosage of relaxants. He associated these results with the lowered blood acidity which he found almost invariably accompanied controlled respiration. This work has been supported by Gray and Geddes (1959) who drew attention to the appearance of slow wave activity in the e.e.g. during nitrous oxide, oxygen relaxant, controlled respiration anaesthesia and produced some evidence that this was attributable to hyperventilation. They also pointed out that the work of Bonvallet and Dell (1956) suggested that the blood tension of carbon dioxide had an important influence on the activity of the reticular area of the mid-brain, and they suggested that depression of the reticular activating system under conditions of respiratory alkalosis might account both for the appearance of slow waves and for the increased potency of nitrous oxide which was clinically evident.

Ever since Kety and Schmidt (1946) showed that hyperventilation reduced cerebral blood flow, many workers have believed that the cerebral effects of hyperventilation are due to hypoxia. Indeed, Clutton-Brock (1957), who demonstrated a rise in pain threshold in actively hyperventilating subjects, made observations which appeared to support this hypothesis. As hyperventilation is common during the “controlled” respiration of modern anaesthesia, it seemed important to investigate further the cerebral effects of hyperventilation and if possible shed light on their aetiology.

METHOD

The twenty medical students and research workers on whom these experiments were performed were fit males with an age range of 21 to 43 years; only two subjects exceeded 30 years of age.

Passive hyperventilation was produced with a Technicon Huxley pump and thoraco-abdominal cuirass (fig. 1). When the pump was set to apply to the cuirass positive and subatmospheric pressures of ± 40 cm of H2O at a rate of 24/min, this respirator proved capable of ventilating conscious subjects with very high minute volumes. It was realized that these conditions of hyperventilation only approximated to those present in the hyperventilation of anaesthesia, but other methods were not practicable with conscious volunteers.

The ventilation achieved was measured as the expiratory minute volume using the anemometer described by Wright (1955). Using the method of Brooks and Wynn (1959), arterialized venous blood was drawn into heparinized syringes, the deadspace of which had been filled with neutral oil. The pH of this blood was measured anaerobically at 38°C in a micro-flow glass electrode system (E.I.L.) by means of a potentiometer (E.I.L. model 33C) and an electrometer having a high sensitivity and stability (E.I.L. model 33B). The Pco2 was estimated using the anaerobically separated plasma by a modification of Astrup’s (1956) interpolation method (Robinson and Pimbblet, 1961).

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**Observations.**

During the course of the experiments the following observations were made:

**Pain threshold.** The pain threshold was measured by the application of a spring-loaded plunger rod to the tibia. The pressure necessary to cause the subject to show evidence of pain was recorded in kilogrammes on a sliding scale affixed to the plunger.* Using this method, two distinct responses to the stimulus were obtained.

The subject was asked to raise his hand when the pressure became painful. This was designated the “pain threshold”.

When the pressure was continued evidence of unbearable pain was shown by facial wincing or withdrawing of the leg. This was designated the “pain response”. Dundee and Moore (1960) working independently described an almost identical method and reported on its accuracy.

The initial “threshold” response fell with constant repetitive distraction such as the ticking of a metronome or the regular rhythm and noise of the respirator. The second “response” reading was found to be unaltered by distraction and therefore this alone was used during the course of the experiments.

Towards the end of the experiments when, as will be shown later, a plateau of rise in pain threshold had been established, the effects were observed of the inhalation of the following:

Concentrated ammonia vapour.
0.18 ml of amyl nitrite.
A very high flow of oxygen through an open circuit for 4 minutes.

**Fundal vessels.** Direct retinoscopy during hyperventilation showed constriction of the retinal vessels. It was considered that changes in the retinal vessels might well mirror those in the vessels of the brain and therefore fundal examination was carried out from time to time during the experiments.

**Cerebral function.** Other changes in cerebral function were difficult to estimate. However, some assessment of mental agility could be made by exercises in simple mental arithmetic and by conversation. During the experiments, there were signs of changes in the mental attitude of the

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*This apparatus is manufactured by Messrs. Baird and Tatlock Ltd.*
subject and the help of a psychiatrist was enlisted to elucidate these effects.

RESULTS

Pulmonary ventilation achieved.
The pulmonary ventilation achieved varied greatly from subject to subject and from period to period. Most of these subjects achieved values for pulmonary ventilation of 30 l./min or more; two reached the remarkably high figure of 50 l./min. The values and changes in pulmonary ventilation produced in these subjects are discussed elsewhere in greater detail by Robinson (1960). However, in no case in this series was the ventilation value lower than 17 l./min.

\[ \text{pH and Pco}_2 \text{ values.} \]
At the end of 1 hour this method of hyper-ventilation in these subjects gave a mean pH value of 7.69 ± 0.17. Values for pH as high as 7.88 and 7.76 were recorded in two subjects, but in one subject, who had a barrel-shaped and rigid thoracic cage, the comparatively low figure of 7.52 was obtained. Similar but reciprocal changes in the Pco_2 were recorded; all but one case reached values of 23.5 mm Hg or lower, the lowest value recorded being 12.5 mm Hg and the highest being 27.5 mm Hg. A further description of the Pco_2 changes are given by Robinson (1960).

Pain response.
In all cases the pain response rose, the average increase in pressure required to elicit a response being 7 kg ± 2. In six subjects the rise was below the average and in eight it was above, but these readings could not be related to greater or lesser changes in pH values (fig. 2).

To demonstrate the direction and extent of the changes in pain response during hyperventilation, all the pain response and pH readings for the twenty subjects are presented as a semilogarithmic plot in figure 2. This includes the basal levels of pain response which show the usual trimodal distribution of normal, hyper- and hyposensitive responses. It was interesting to note that the obviously apprehensive subjects had high initial pH values, probably due to their emotional over-ventilation whilst awaiting the start of the experiments.

It can also be seen from figure 2 that the pain threshold rose with hyperventilation until pH values around 7.55 were reached. Further increases in pH above this value did not raise the pain threshold to any appreciable degree.

Inhalation of ammonia, amyl nitrite and oxygen.
The effect of the inhalation of concentrated ammonia vapour was the same in all cases. It caused an immediate fall in pain response which quickly returned to within 1 or 2 kilogrammes of the original value. Examination of the optic fundus at this time showed the retinal vessels to be maintaining the vasoconstriction.

The immediate effect of the inhalation of amyl nitrite was exactly the same as that of concentrated ammonia vapour. There was an immediate fall in pain response to levels within 1 or 2 kilogrammes of the pressure originally required.

The pain response was tested again at a time when the amyl nitrite had caused intense facial vasodilatation and dilatation of the retinal vessels but the blood pressure had returned to within 10 mm Hg of its initial value. At this time the pain response in eight subjects had returned to within 1 kilogramme of the pre-amyl nitrite level and in twelve instances it had increased above this level.

In all except two cases the administration of ammonia and amyl nitrite caused a disturbance in respiratory rhythm due to the irritant nature of the vapours. In three of the subjects estimation of the acid-base changes after inhalation of these vapours showed that there was a fall in pH value of between 0.1 and 0.08 pH units.

The administration of 100 per cent oxygen for 4 minutes caused no change in pain response or fundal vessels. Indeed, the only effect observed occurred in three subjects who became very sleepy during its administration.

Other cerebral changes.
All these subjects showed a diminution in mental agility. Simple mental arithmetical tests using figures of unity were performed slowly but correctly; however, problems involving figures over unity in most instances resulted in erroneous answers. Several subjects found that, although anxious to help by answering such questions, the problems were too involved for coherent thought.

All except one of the subjects commented on the fact that they felt "rather odd" and all showed an amiability similar to that of mild
alcoholic intoxication. Six subjects showed pronounced facetiousness and a tendency to hilarity.

The subjects were considered by a psychiatrist to have all their aggressive tendencies depressed. Furthermore, although on arrival in the laboratory for the experiments the volunteers were often apprehensive, towards the end of the experiment they became very co-operative and often volunteered spontaneously for further and even more traumatic experiments.

**Visceral sensation.**

A diminution in visceral perception seemed to occur. Three volunteers started the experiments with full bladders and all complained initially of an increased discomfort as the respirator applied intermittent pressure to the abdomen. After 10 to 15 minutes hyperventilation, when a respiratory alkalosis had been established, all three became unaware of bladder discomfort and it must be remembered that the experiments proceeded for at

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**Fig. 2**

Composite plot of pain response and blood pH compiled from values obtained before and during the experiments.

For clarity the pain responses have been plotted as log values although the flattening of the curve would be still evident on normal cycle graph paper.
least 1 hour. Acute vesical discomfort returned to these subjects within a short time of the cessation of hyperventilation.

**DISCUSSION**

It has been proposed that the cerebral effects accompanying a respiratory alkalosis are attributable to cortical hypoxia. This stems from the work of Kety and Schmidt (1946) who measured cerebral blood flow and oxygen uptake during active and passive hyperventilation. They found that the cerebral blood flow was reduced by one-third and that there was an increase in the difference between the oxygen tensions of arterial and cerebral mixed venous blood. Although they had no direct information, Kety and Schmidt suggested that the oxygen tension of the venous blood draining the cerebrum mirrored that of the cortical cells and that the observed fall in this value therefore indicated a degree of cerebral hypoxia.

Sugioka and Davies (1960) lent support to this suggestion by their findings that the oxygen tension in the cerebral cortex of dogs fell from a normal level of 8–15 mm Hg to 3–5 mm Hg when these animals were passively hyperventilated. These measurements were made using a modification of the Clarke (1953) oxygen electrode. Although the polarizing voltage was delivered intermittently at a rate of 8 pulses per second, since the work of Glover (1959) this rate must be regarded as too high and must have led to a rate of oxygen consumption at the electrode greater than that which could have been replaced by the diffusion of oxygen through the cortical tissues. For this reason, therefore, the figures for cortical oxygen tension produced by Sugioka and Davies would be too low and cannot be regarded as absolute values—they only indicate relative changes.

The lowest tension at which cortical tissue can utilize oxygen is not known, but further consideration of the work of Kety and Schmidt sheds some light on this subject. Their results show that during passive hyperventilation the oxygen uptake of the brain remained the same in spite of the great reduction in cerebral blood flow and the increase in cerebral arteriovenous oxygen difference. Furthermore, the results obtained during active hyperventilation show that the brain was able to increase its oxygen consumption, in spite of the reduced cerebral blood flow and greater cerebral arteriovenous oxygen difference. It is inconsistent to assume that cerebral hypoxia occurred during their experiments, because the oxygen consumption of the brain during passive hyperventilation was shown to be the same as the consumption at rest, yet, when an increased oxygen demand of the brain occurred as during the mental concentration necessary for active hyperventilation, this was satisfied by an increase in oxygen uptake.

The conclusion of Clutton-Brock (1957), that the analgesia produced by hyperventilation was due to cerebral hypoxia, was based upon the fact that in actively hyperventilating subjects the administration of oxygen lowered the pain threshold as did also the administration of a vasodilating substance—amyl nitrite.

The work reported here does not support the conclusion that the cerebral effects of hyperventilation are due to cerebral hypoxia for the following reasons.

In these experiments the administration of amyl nitrite, although causing an initial decrease in pain response, ultimately resulted in a considerable increase. An exactly similar initial decrease was achieved by the inhalation of strong ammonia vapour.

It is suggested that the initial lowering of the pain response to nearly normal levels after the administration of amyl nitrite and ammonia was due to the pungent nature of their vapours. This was, in fact, strong enough to cause disturbance of respiratory rhythm and consequent lowering of the pH and elevation of Pco₂. These changes would in themselves result in some lowering of the pain response, but when considered in relation to the overall pain response/pH curve (fig. 2), it could be seen that they were insufficient to explain the return of the pain response to normal.

It seems more likely that the lowering of pain response with pungent vapours is due to a reflex stimulus of cerebral activity ("increased arousal") arising from its irritant action on the upper respiratory tract. It is presumed that this is much the same effect as that which "sal volatile" produced when prescribed for fainting attacks.

Furthermore, examination of the fundal vessels, which might be thought to reflect the reactions of the cerebral vessels, showed release of vasocon-
striction with amyl nitrite but maintained their vasoconstriction with ammonia. After the initial fall following amyl nitrite, the pain response returned to its former level or even higher although at this time the fundal vessels were still dilated and the blood pressure was within 10 mm Hg of normal. It seems unlikely, therefore, that there was any reduction in cerebral blood flow at this time despite the elevated pain response.

If cortical hypoxia is the cause of the raised pain response during hyperventilation, then oxygen inhalation might be expected to raise the oxygen tension of arterial blood and that of the cerebral cortex, thus reducing the analgesia. However, in these experiments, contrary to the findings of Clutton-Brock (1957), oxygen inhalation did not have this effect.

Finally, it was noteworthy that the other cerebral effects noted cannot be correlated with those known to accompany the hypoxia of high altitude flying. During high altitude flying headache, aggressiveness and over-confidence are predominant symptoms if cerebral hypoxia is present. The subjects of these experiments never experienced headache and, far from showing aggressive or reckless tendencies, became very co-operative and amiable.

If the cerebral effects of passive hyperventilation are not due to hypoxia they could be due to the high ambient pH of the cerebral blood flow, or the low Pco$_3$ level, but more likely a combination of the two factors.

Some support for this hypothesis is lent by the work of Bonvallet and Dell (1956) who showed that low carbon dioxide tensions produced by hyperventilation caused a marked decrease of the frequency of discharge from the reticular activating system and in certain animals caused complete depression.

CONCLUSION

The advantages of hyperventilation as an adjuvant to anaesthesia have been described by many authors and amongst the advantages claimed have been a reduction in the dosage of anaesthetic agents employed and an increase in their potency.

This investigation shows that these effects are probably due to the production of general analgesia and from the depression of other cerebral functions which results during passive hyperventilation. The suggestion that these effects are due to a reduction in cerebral blood flow and a degree of cerebral hypoxia is shown to be an hypothesis with little foundation. It is suggested that the cerebral effects can be accounted for by the changes in Pco$_3$ and pH values alone.

SUMMARY

Twenty male subjects were passively hyperventilated using a cuirass type of respirator. The pain response as measured by the application of a spring-loaded plunger to the tibia was shown to rise during hyperventilation until blood pH values of around 7.55 were reached.

It was suggested that as the retinal vessels probably behave in a similar manner to those of the brain, observation of them during the experiments, would give useful information. They were seen to constrict during hyperventilation. A fall in the elevated pain response was not demonstrated when vasodilation of the retinal vessels was produced by inhalation of amyl nitrite and when the blood pressure was at a normal level, nor did it fall during inhalation of oxygen. An initial decrease in pain response after amyl nitrite was noted and thought to be due to the irritant nature of its vapour as a similar effect was observed after inhalation of sal volatile.

Other cerebral effects observed were a loss of mental agility, a depression of aggressive tendencies, a loss of visceral sensation and the amiability characteristic of a mild alcohol intoxication.

As there was no decrease in analgesia with the production of retinal vasodilatation by amyl nitrite or by inhalation of oxygen it is considered unlikely that the cerebral effects are due to cerebral hypoxia resulting from the constriction of the cerebral vessels. It is suggested that the cerebral effects can be accounted for by changes in pH and Pco$_3$ values alone.

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REFERENCES


BOOK REVIEW


This second edition is some thirty pages longer than the first. This increase in length and the revision of much of the text has been made desirable owing to the increasing interest that has been shown in the complications of anaesthesia since the publication of the first edition some five years ago. Dr. Keating admits that his limited experience of anaesthesia has not enabled him actually to be present at all the accidents that he describes and so he has had to supplement this deficiency by the experience of others. This has proved no detriment as he has made himself intimately acquainted with the reports of them sent to him. Indeed the outstanding impression of the book as a whole is the amount and quality of the thought that Dr. Keating has put into the consideration of his subject. There is a short chapter at the end dealing with medico-legal matters which will prove of immense help to the anaesthetist faced with the necessity of appearing in the coroner's court. From the point of view of accuracy a new proof-reader for the references is required.

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