ACCIDENTAL SEVERE HYPERCAPNIA DURING ANAESTHESIA
A Case Report and Review of some Physiological Effects
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SUMMARY
A case report is presented which describes the development, recognition and correction of gross hypercapnia occurring during anaesthesia. The cause of hypercapnia was a high concentration of carbon dioxide in the inspired gas caused by the accidental opening of the control valve for carbon dioxide. Certain structural features of the anaesthetic apparatus facilitated this, and the construction of the Rotameter resulted in the bobbin being concealed at the top of the tube. Recognition of the condition would have been difficult without analysis of arterial blood. The patient did not appear to suffer any overt harm from the incident or its rapid correction by withdrawal of the carbon dioxide from the inspired gas. The aetiology and effects of gross hypercapnia during anaesthesia have been reviewed and special attention has been paid to the problem of measurement of the acid-base abnormality.

Little is known about the effects of very high tensions of carbon dioxide in man. Deliberate experimentation is scarcely possible and accidental cases of gross hypercapnia are very seldom supported by the data which are of particular value in defining the dangers of the condition. There has been much resort to animal experimentation, but the results of these studies must be interpreted with caution as species differences are known to be important in this field.

We report here a single case of severe hypercapnia caused by the accidental inhalation of carbon dioxide. It was fortunate that an arterial blood sample was taken and analyzed before the diagnosis was made and therefore the level of arterial Pco₂ is known and may be related to the clinical signs observed in the patient. The actual level of PaO₂ is one of the highest levels in arterial blood of man which has come to our notice.

CASE REPORT
R.F.S., a 60-year-old male, was admitted for exploratory laparotomy following an examination which had confirmed the presence of an abdominal swelling which had been present for about 10 months. He had a 25-year history of dyspepsia, with recent onset of nausea and epigastric discomfort. The abdominal swelling had been tentatively diagnosed as either a secondary carcinoma in the liver or a cirrhotic liver. The patient stood 183 cm high and weighed about 73 kg. He was an active man, accustomed to drinking about 3 pints of beer per day, and had had no previous serious illness. He had rhinophyma and facial telangectasia which gave him a cyanotic appearance under normal conditions. He had an irregular pulse which an electrocardiogram had shown to be due to occasional ventricular ectopic beats. His blood pressure was 160/90 mm Hg, and his haemoglobin concentration was 17.2 g/100 ml.

He was premedicated with papaveretum 10 mg, and dehydrobenzperidol 10 mg, given intramuscularly. In the anaesthetic room, his pre-operative systolic blood pressure was 110 mm Hg, and his pulse rate was about 80 beats/min. At 08.50, anaesthesia was induced with 250 mg of thiopentone sodium, and a slow circulation time was noted. Following the intravenous injection of suxamethonium 50 mg, a cuffed oral endotracheal tube was inserted and connected to a Manley ventilator which was supplied with nitrous oxide (7 L/min) and oxygen (3 l./min) and set to provide a tidal volume of 800 ml. The anaesthetic record of this patient is shown in figure 1.

It was immediately noted that the ventilator inflation frequency appeared to be higher than it should be for the tidal volume setting and the fresh gas flow in use. Spontaneous ventilation returned rapidly and tubocurarine 30 mg was administered intravenously.

When an intravenous infusion had been established, the ventilator frequency was checked and found to be 15 b.p.m. instead of 12.5 b.p.m., suggesting that the fresh gas flow was 12 l./min instead of the flow of 10 l./min shown by the Rotameters. A Wright respirometer was then used to check the expired minute volume, and this was confirmed to be 12
Attention was then distracted from this puzzling state of affairs by the appearance of the patient. Cyanosis had deepened alarmingly, and the pulse rate had increased to about 100 b.p.m. and had become more irregular. Systolic blood pressure was 140 mm Hg. The patient's brow felt damp although no frank sweat could be seen. He was beginning to show signs of straining against the ventilator, so an increment of tubocurarine 10 mg was given.

Bearing in mind the patient's normal appearance, and the evident inadequacy of muscular relaxation, it was considered that the cyanosis was peripheral rather than central. Its intensity, however, coupled with the increasing pulse irregularity and the clamminess, gave rise to some anxiety and an arterial blood sample was drawn for analysis of blood gas tensions, so that a baseline would be available before proceeding with any further measures. By the time a heparinized syringe had been obtained, the patient's colour had improved considerably, and his face appeared less cyanosed than before. The muscular relaxation was adequate but there was no obvious decrease in the irregularity of the pulse. A blood sample was taken from a radial artery through a fine needle but since this looked more desaturated than would have been expected from the patient's improved appearance, a further sample was obtained from a femoral artery at 09.05. However, this sample, which was sent to the laboratory for analysis, looked just as desaturated as the previous one.

Limb electrodes had been placed for monitoring the electrocardiogram using a Videograph Phase II (Medical and Industrial Equipment Ltd.), and in view of the improved appearance of the patient he was moved into the operating theatre and laparotomy was commenced. A few minutes later a verbal report of the blood gas analysis was received. The pH was reported as 6.86 and this was regarded with incredulity by the anaesthetist until, a moment later, the bobbin of the carbon dioxide Rotameter was observed to descend into view from behind the manufacturer's trade mark at the top of the tube. The reported $P_{CO_2}$ value of
248 mm Hg (table I) was then understandable, though the Pao₂ of 104 mm Hg did not seem to accord with the apparent desaturation of the blood.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample B after reduction of Pco₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>09.05</td>
</tr>
<tr>
<td>pH</td>
<td>6.860</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>248.0*</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>103.5</td>
</tr>
<tr>
<td>Standard Bicarbonate (m.equiv/L)</td>
<td>17.2</td>
</tr>
<tr>
<td>Base Excess (m.equiv/L)</td>
<td>-9.4</td>
</tr>
</tbody>
</table>

*This value for Pao₂ is not corrected for non-linearity of the log Pco₂/pH plot (see text).

The carbon dioxide flow was turned off immediately, and the nitrous oxide flow was reduced to 6 l./min. The frequency of the ectopic beats then decreased towards the end of the operation and there was no further cause for anxiety in relation to anaesthesia. A further sample was withdrawn at 09.35, the results of which are shown in table I. Laparotomy revealed a liver which was invaded by secondary carcinoma, the primary being found in the sigmoid colon which was resected. A further 5 mg tubocurarine was given during the operation and gallamine 40 mg was required for abdominal closure. After surgery had finished, atropine 1.2 mg was given in divided doses followed by neostigmine 2 mg also in divided doses of 0.5 mg. Spontaneous ventilation returned at this stage, but a further 3.0 mg neostigmine was required before adequate ventilation was achieved. There were no post-operative sequelae, and the patient appeared to be in good condition on the following day.

On checking the anaesthetic machine it was found that only a very light touch was necessary to turn the carbon dioxide flow control knob, and that only a third of a revolution was required to obtain the maximal flow of carbon dioxide. A dangerous feature of the machine was that the bobbin of the carbon dioxide Rotameter disappeared behind the manufacturer's trade mark at the top of the tube. The manufacturer has now rectified this defect. It was estimated that the patient received about 35 per cent carbon dioxide for approximately 30 minutes. In this particular case the fine adjustment control for carbon dioxide was either opened before the administration of the anaesthetic or was accidentally opened during the induction of anaesthesia. It has not proved possible to establish when this occurred. However, if the control had been opened before the commencement of the anaesthetic, the considerable volume of the gas circuit could well have been filled with 100 per cent carbon dioxide which would result in a very high concentration of carbon dioxide in the inspired gas for some time after the oxygen and nitrous oxide flow had commenced.

A second laparotomy was performed on the same patient six months later, in order to cannulate a branch of the left hepatic artery for perfusion of cytotoxic drugs. The course of anaesthesia was uneventful.

**DISCUSSION**

*Aetiology of gross hypercapnia.*

Hypercapnia with Pco₂ values in excess of 90 mm Hg is unlikely to occur in patients breathing air, since the concomitant degree of hypoxia would be incompatible with the survival of the patient (Refsum, 1963, McNicol and Campbell, 1965). Hypercapnia with Pco₂ in excess of 100 mm Hg may therefore be considered as an iatrogenic condition, as it can only occur if a patient is breathing oxygen-enriched air, or is exposed to high concentrations of carbon dioxide in the inspired gas.

Three main causes of gross hypercapnia may be distinguished.

Firstly, the patient may have inadequate ventilation, which will result in a slow rise of Pco₂, finally limited by the actual level of alveolar ventilation. In theory the Pao₂ could rise to several hundred millimetres of mercury, but in fact reports of levels exceeding 100 mm Hg are quite rare. During thoracic surgery with assisted ventilation, levels of up to 133 mm Hg were reported by Beecher and Murphy (1950) and up to 170 mm Hg by Taylor and Roos (1950). In an excellent review of earlier work, Ellison, Ellison and Hamilton (1955) reported a maximum level of 236 mm Hg, and Hornbein (1963) reported a level of 235 mm Hg in a small child with bronchopneumonia, despite artificial ventilation.

The extreme degree of hypoventilation is apnoea which may be prolonged if mass-movement oxygenation ("diffusion respiration") is employed. By this means, Frumin, Epstein and Cohen (1959) allowed patients to attain levels of Pao₂ estimated to be in excess of 200 mm Hg, at a rate of rise which varied between 2.7 and 4.9 mm Hg per minute. This rate is in agreement with
the value found by Sullivan, Patterson and Papper (1966).

The second cause of gross hypercapnia is reinhalation of exhaled carbon dioxide, and this was the sole cause in the important case reported by Schultz and associates (1960). In their case, the patient rebreathed carbon dioxide as a result of missing valves in a circle absorber system which prevented the exhaled carbon dioxide from being absorbed by the soda-lime, causing a rise of $P_{CO_2}$ to $234$ mm Hg. It seems likely that defective carbon dioxide absorption or excessive apparatus deadspace may well have contributed to other cases of gross hypercapnia in whom the level of $P_{CO_2}$ could otherwise only be explained by an incredibly low alveolar ventilation. The patients described by Birt and Cole (1965) breathed spontaneously through a facepiece connected to a circle absorber system with a halothane vaporizer within the circle. Although high minute volumes of ventilation were recorded, the tidal volumes were low due to tachypnoea, and were associated with levels of $P_{aO_2}$ up to $160$ mm Hg. Thus the hypercapnia was probably due to excessive apparatus deadspace, and could have been largely reduced by the use of endotracheal intubation. The rate of rise of $P_{CO_2}$ during rebreathing is determined by the rate of production and the body storage capacity for carbon dioxide, and is thus similar to that occurring during hypoventilation and apnoea. It is unlikely to exceed $6$ mm Hg per minute.

The third cause of gross hypercapnia is the inhalation of exogenous carbon dioxide. This differs from the other causes in that the extent or rate of rise of $P_{CO_2}$ is not limited by metabolic production of carbon dioxide. The height to which the $P_{CO_2}$ can rise under these circumstances is limited only by the atmospheric pressure, and a level of $600$ mm Hg has been attained in dogs (Graham, Hill and Nunn, 1960), and no doubt could be attained in man. Meduna (1950) recounts the inhalation of 30 per cent carbon dioxide for therapeutic abreaction, during which the $P_{CO_2}$ was found to rise within less than a minute to levels in excess of $200$ mm Hg.

The case we have reported falls into this third category, and is perhaps the first reported case to have occurred during anaesthesia, although similar cases have no doubt happened often enough in the past without having been reported.

**Effects of gross hypercapnia.**

The important questions are the means of diagnosing gross hypercapnia, definition of the dangers of the condition, and establishment of the best method of treatment.

The clinical signs of hypercapnia may be easily misinterpreted if they occur under conditions when gross hypercapnia would be unexpected. It is of interest, in the patient described here, that the first sign which distracted the attention of the anaesthetist was marked cyanosis, a feature which was unexpected in view of the apparent adequacy of the oxygen supply.

**Oxygen carriage by blood.** At the degree of combined metabolic and respiratory acidosis existing in the blood of the patient, the oxygen dissociation curve would be displaced to the right. The magnitude of this Bohr effect may be predicted from the data available on the normal oxygen dissociation curve, or it may be experimentally determined under in vitro conditions. As the oxygen saturation of the original blood sample was not measured, we can only make an estimate of the desaturation which might be expected at a $P_{CO_2}$ of $250$ mm Hg and a $P_{aO_2}$ of $104$ mm Hg. Our experimentally determined oxygen dissociation curve at a blood $P_{CO_2}$ of $250$ mm Hg is shown in figure 2, in which it is compared with the standard dissociation curve at a $P_{CO_2}$ of $40$ mm Hg (Severinghaus, 1966) and with the curve at a $P_{CO_2}$ of $250$ mm Hg and a Base Excess of $-9.4$ m.equiv/l. predicted from the nomogram of Kelman and Nunn (1966a). At an arterial $P_{O_2}$ of $104$ mm Hg, the experimentally determined saturation and that predicted from the nomogram would have been about 90 per cent. Under the lighting conditions of the anaesthetic room it is usual to be able to detect this degree of desaturation, both in the patient himself and the withdrawn blood in the syringe (Kelman and Nunn, 1966b).

**Circulatory effects of gross hypercapnia.** The improvement in the colour of the patient following the administration of the supplementary increment of tubocurarine may have been due to many factors related to cardiovascular performance. The increment was given because the patient was straining against the ventilator, an observation which was made after becoming aware of the increased cyanosis. Peripheral circulatory stasis...
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\[ P_{CO_2} : 40, \text{ base excess : 0} \]
\[ P_{CO_2} : 250, \text{ base excess : -9.4} \]

**Fig. 2**

In vitro oxygen dissociation curves during severe hypercapnia. The continuous line represents the normal dissociation curve at a \( P_{CO_2} \) of 40 mm Hg (after Severinghaus, 1966). The interrupted line represents the dissociation curve at a \( P_{CO_2} \) of 250 mm Hg and a base deficit of -9.4 m.equiv/l. derived from the nomogram described in the text. The open and closed circles are experimentally determined values of \( PO_2 \) and \( SO_2 \) at a \( P_{CO_2} \) of about 250 mm Hg.

and a reduced cardiac output during the period of straining may have contributed to the cyanosis at this stage, in addition to the desaturation of the arterial blood. Regional blood flow may be markedly altered by increases in \( P_{CO_2} \), and of particular interest in relation to this patient is the response of skin blood flow to hypercapnia. McArdle and colleagues (1957) showed that skin blood flow increased during periods of raised \( P_{CO_2} \), and it may be expected that some of the improvement in the colour of the patient may have been due to improved flow through the telangiectatic facial vessels.

The role of increased cardiac output in enhancing the flow of blood through skin is not so clear. Investigations during nitrous oxide anaesthesia (Prys-Roberts and Kelman, 1966) have shown that hypercapnia to \( P_{CO_2} \) values above 90 mm Hg is associated with elevated levels of cardiac output, and that the circulation is in a hyperdynamic state. Caution is needed, however, in extrapolating these findings to the state of gross hypercapnia found in this patient. Severinghaus, Mitchell and Nunn (unpublished observations) demonstrated that increasing the \( P_{CO_2} \) to levels in excess of 300 mm Hg in dogs, caused a progressive depression of cardiac output. Even at a \( P_{CO_2} \) of 390 mm Hg, however, they found the cardiac output was only depressed to 70 per cent of the value during eucapnia. It is therefore difficult to assess the
level of hypercapnia in man at which the augmented filling of the right atrium caused by raised venous pressures is balanced by the depression of myocardial contractility caused by the direct action of carbon dioxide on the heart (Manley, Nash and Woodbury, 1964).

The development of cardiac arrhythmias during anaesthesia at high Pco₂ appears to be influenced by the nature of the anaesthetic agents used, but the position is still not entirely clear. Disorders of cardiac rhythm caused by high concentrations of carbon dioxide have been variously described in anaesthetized man by Lurie and colleagues (1958) and Price and colleagues (1958) using cyclopropane, and Black and colleagues (1959) using halothane. These workers found a threshold of Pco₂ above which arrhythmias always occurred, the mean level being about 90 mm Hg for patients under halothane anaesthesia, although some patients developed arrhythmias at considerably lower levels of Pco₂. Birt and Cole (1965) described arrhythmias during closed circuit halothane anaesthesia, which were alarming and bizarre, yet they occurred at relatively low levels of hypercapnia. It would appear from their study that the threshold for arrhythmias may have been strongly influenced by the high concentration of halothane to which their patients were exposed.

McDonald and Simonson (1953) and McArdle (1959) have both reported normal electrocardiographic appearances in the majority of their subjects breathing 30 per cent carbon dioxide in oxygen, but also demonstrated a variety of abnormalities of both rhythm and voltage of the electrocardiograph of the other subjects. These abnormalities have also been described in detail by Altschule and Sulzbach (1947).

In their study of graded hypercapnia in man anaesthetized with nitrous oxide, Prys-Roberts and Kelman (1966) were unable to demonstrate any abnormality of the e.c.g. in any patient, the maximum Pco₂ recorded being 94 mm Hg.

In the matter of arrhythmias, the responses of dog and man appear to be quite different. Graham, Hill and Nunn (1960) raised the arterial Pco₂ in a series of dogs to about 550 mm Hg and found no disorders of cardiac rhythm in the presence of either cyclopropane or halothane. Apart from the very important species difference between dog and man, it seems certain that the effect of carbon dioxide on the myocardium and its conduction system is strongly influenced by the type of anaesthetic agent used, and by the blood concentration of that agent.

The abnormalities of the e.c.g. were unfortunately not recorded in the case presented here and interpretation of the oscilloscope trace at the time was very difficult in view of the pre-existing abnormality in this patient. It is of great interest, however, that in spite of the rapid reduction of Pco₂ to the normal level, no further abnormalities of rhythm were induced by this manoeuvre. This finding contrasts sharply with the widely quoted work of Brown and Miller (1952), who reported that ventricular fibrillation may follow the sudden reduction of high Pco₂ in dogs. Their findings, however, have not been confirmed by other workers. Graham, Hill and Nunn (1960) and Millar (1960) were unable to produce ventricular fibrillation despite precipitous falls of Pco₂ in dogs ventilated with oxygen after a prolonged period of gross hypercapnia. Prys-Roberts, Kelman and Nunn (1966) were also unable to demonstrate any change of the e.c.g. in a series of anaesthetized patients whose arterial Pco₂ was reduced from about 80 mm Hg to less than 20 mm Hg over a period of 5 minutes. It has been suggested that the observations made by Brown and Miller may have been precipitated by concomitant "diffusion" hypoxia caused by ventilation with air in the presence of elevated levels of Pco₂. Some evidence in favour of this hypothesis was presented by McArdle (1959), who demonstrated atrial extrasystoles occurring in patients breathing air following the administration of carbon dioxide (30 per cent) in oxygen.

Arterial pressure usually rises as the Pco₂ increases in both conscious and anaesthetized man (Price et al., 1960), but in dogs, although there is an initial rise in blood pressure as the Pco₂ rises (Millar, 1960), gross hypercapnia causes a decline in blood pressure as the cardiac output falls, and hypotension is a common feature of death in supercarbia (Graham, Hill and Nunn, 1960). There is general agreement that a fall in arterial Pco₂ is accompanied by a fall in blood pressure, paralleled with a fall in cardiac output (Prys-Roberts and Kelman, 1966).

Changes in pulmonary circulation occur in response to hypercapnia, but such changes have been
shown by Bergofsky, Lehr and Fishman (1962) and Linde, Simmons and Lewis (1963) to be pH-dependent. They demonstrated that an increase in pulmonary vascular resistance did not occur if the pH was kept constant during a rise of Pco₂.

Acid-base equilibrium. The greatest stress imposed on the homeostatic mechanisms responsible for the defence of blood and tissue neutrality is that produced by gross hypercapnia. The limits of tolerance of such extreme acidosis are difficult to define in view of the varying degrees of combined respiratory and non-respiratory acidosis. The biochemical indices of the non-respiratory component of acid-base state, Standard Bicarbonate and Base Excess (Astrup et al., 1960) indicate that acute changes of Pco₂ cause an apparent metabolic or non-respiratory acidosis. Such a metabolic acidosis was first suggested by Holaday, Ma and Papper (1957), who used whole blood buffer base as a measure of the non-respiratory component. Two points of interest arise in relation to the patient described. The first relates to the validity of extrapolating the in vitro carbon dioxide equilibration curve used in the determination of Pco₂ by the micro-equilibration method described by Siggaard-Andersen and associates (1960). The second is concerned with the relationship between the in vivo and in vitro carbon dioxide equilibration curves.

The interpolation method of measuring Pco₂ is based on the measurement of the pH of the sample under anaerobic conditions, followed by measurement of the pH of the same blood sample equilibrated with two gas mixtures having respectively higher and lower Pco₂ values than the blood sample. In clinical practice, this can be achieved by the use of gas mixtures containing approximately 3 and 10 per cent carbon dioxide, representing Pco₂ values of about 20 and 75 mm Hg respectively. The method is based on the assumption that over this range of Pco₂, the relationship between log Pco₂ and pH is sensibly linear. That this is so has been demonstrated by Brewin and associates (1955), Siggaard-Andersen (1964), and Kelman, Coleman and Nunn (1966), though Siggaard-Andersen pointed out that this is only an approximation to linearity over a relatively narrow range of Pco₂, and that as Pco₂ increases, the in vitro log Pco₂/pH curve deviates from linearity in the direction of acidosis. As gas mixtures containing about 40 per cent carbon dioxide are not routinely available for use with the micro-equilibration unit in our laboratory, it was considered necessary to evaluate any possible error in making an extrapolation of the in vitro line to the range including a Pco₂ of more than 200 mm Hg. Figure 3 shows the mean of 21 in vitro carbon dioxide equilibration lines (ABCD) determined by measurement of the pH of the same blood equilibrated with four gas mixtures containing 2.7, 10.8, 22.3 and 35.8 per cent carbon dioxide. The linear extrapolation of the line AB to E (the point of intersection with the measured pH of 6.86) gives a value of 248 mm Hg for Pco₂, whereas the same pH intercepted on the true in vitro curve would give a value around 200 mm Hg. For the clinical evaluation of the patient's condition, this error in measurement is of little significance, although for the purpose of comparison of the in vivo and in vitro curves, such an error may be important. Although the Pco₂ value of 248 mm Hg was reported by the technical staff of our laboratory, the actual

![Diagram showing pH vs. Pco₂](https://example.com/diagram.png)
value was probably in excess of 200 mm Hg, but the precise value cannot be determined in retrospect. It would seem that measurement of the total carbon dioxide content of the whole blood is the only satisfactory method for the exact determination of high carbon dioxide levels under normal laboratory conditions. However, the calculation of Pco₂ from carbon dioxide content is difficult under these circumstances as the value of pK' may alter.

The slope of the in vivo carbon dioxide equilibration curve ($\Delta \log$ $P_{CO_2}/\Delta pH$) for this patient, between $P_{CO_2}$ values of 31 and 248 mm Hg was determined to be $-1.68$, and the mean in vitro slope was $-1.88$. The ratio of these slopes (in vivo/in vitro) was $0.89:1.0$, which agrees well with the experimentally determined ratio of $0.91:1.0$ obtained over a smaller range in a series of anaesthetized patients by Prys-Roberts, Kelman and Nunn (1966).

The values in table I indicate that at a $P_{CO_2}$ of 250 mm Hg there was a base deficit of 9.4 m.equiv/1., although this deficit was halved when the $P_{CO_2}$ returned to the normal level. This apparent metabolic acidosis is an indication of the artefact caused by the difference between the response of whole blood and the whole body to changes of $P_{CO_2}$, first described by Shaw and Messer (1932). They demonstrated that the reduced bicarbonate ion concentration in whole blood withdrawn from an artery during hypercapnia (interpreted as a metabolic acidosis) was due to the transfer of bicarbonate ions from the blood into the extracellular fluid in response to a concentration gradient across the capillary membrane.

**Effect of gross hypercapnia on respiration.** The need for a second dose of tubocurarine in order to suppress the patient's attempts to breathe against the ventilator, was probably an indication of the effects of excess carbon dioxide on ventilation. Carbon dioxide is a respiratory stimulant, the maximal effect being obtained within the $P_{CO_2}$ range 100–150 mm Hg (Graham, Hill and Nunn, 1960) though at higher levels the stimulation is reduced and eventually carbon dioxide acts as a respiratory depressant. The peak response to $P_{CO_2}$ is, however, dependent on the depth of narcosis and the agent used (Severinghaus and Larson, 1964). Furthermore, it must be accepted that a species difference exists in respect of many effects of carbon dioxide on respiration, and although dogs may become apnoeic when breathing high concentrations of carbon dioxide, cats cannot be rendered apnoeic with carbon dioxide tensions up to 600 mm Hg (Hornbein, personal communication). Clearly, conclusions based on experimental animal work cannot be extended to indicate the likely effect of gross hypercapnia on the respiration of man. It is interesting that the patient described by Schultz and his associates (1960) continued to breathe spontaneously at a $P_{CO_2}$ of 234 mm Hg.

**Central nervous system.** It would seem profitable to review the multiple effects of gross hypercapnia on the central, peripheral and autonomic nervous systems, as the circumstances of this case resemble earlier efforts to produce general anaesthesia by depressing the brain with high concentrations of carbon dioxide.

The original attempts to produce general anaesthesia using carbon dioxide were made by Henry Hill Hickman in 1824, and were repeated using a combination of hypoxia and carbon dioxide administration (Ozanam, 1862), and finally re-investigated in three patients by Leake and Waters (1928) (Waters, 1937) over a century later. The latter authors found that at concentrations which would produce anaesthesia, inhalation of carbon dioxide was associated with convulsions. Woodbury and his colleagues (1958) postulated three levels of brain excitability in response to carbon dioxide inhalation, consisting of a progressive depression up to a $P_{CO_2}$ of about 150 mm Hg, a further stage of excitation at higher carbon dioxide levels, and finally complete suppression of electrical activity at concentrations in excess of 40 per cent. These concepts are in agreement with the findings of Clowes, Hopkins and Simeone (1955) who demonstrated that 30 per cent carbon dioxide would cause total but reversible flattening of the e.c.g. in man. This observation has also been made in dogs (Hopkins, Anzola and Clowes, 1954).

Carbon dioxide is of major importance in the control of intracellular acid-base equilibrium (Adler, Roy and Relman, 1965) and may thus have marked effects upon the metabolism of the cell. Woodbury and Karler (1960) have demonstrated the importance of the effects of carbon dioxide excess on the excitability of neurones. The influence of carbon dioxide on the control of cerebral blood flow has been described by many
authors, notably Kety and Schmidt (1948) and Harper (1965). The latter author demonstrated that the percentage increase in cerebral blood flow in response to a change in Pco₂ was largely dependent on the actual level of arterial pressure, but only investigated a range of Pco₂ from 10 to 100 mm Hg. As the increase was following a sigmoid curve which was flattening at a Pco₂ of 90 mm Hg, it is unlikely that a marked increase in cerebral blood flow would occur at a higher concentration of carbon dioxide. Hypercapnia is also associated with an increase in the cerebrospinal fluid pressure, which may be secondary to increases in cerebral blood flow (Small, Weitzner and Nahas, 1960).

One of the most important effects of carbon dioxide excess is that upon the autonomic nervous system, as a great many of the effects of hypercapnia on other systems are secondary to the response of the sympathetic system. Gross hypercapnia has been shown to be associated with elevated plasma levels of the catecholamines, adrenaline and noradrenaline (Nahas, Ligou and Mehlman, 1960; Millar, 1960). In moderate hypercapnia there is a proportionate rise in the levels of both catecholamines, but at Pco₂ levels in excess of 200 mm Hg, there is an abrupt rise in the concentration of adrenaline in the plasma. Sechzer and his associates (1960) have confirmed these findings over a limited range of Pco₂ in humans.

The relationship between Pco₂ and plasma catecholamine levels may be dependent on the type of anaesthesia used concurrently. Price and his colleagues (1960) found that the catecholamine levels during cyclopropane anaesthesia were higher than those found at similar elevated levels of Pco₂ during halothane anaesthesia, the latter being similar to the response of the unanaesthetized subject. The evidence for the maintenance of elevated levels of plasma catecholamines following the reduction of Pco₂ is conflicting. Millar (1960) found that plasma catecholamine levels diminished rapidly within minutes of a reduction in Pco₂, but this finding is in opposition to those of Heath and Brown (1956) and the general beliefs expressed in the review by Tenney and Lamb (1965).

CONCLUSIONS

Although there are lessons to be learned from the experiences with the case described, they should be self-evident from the case report and the ensuing discussion. It is likely that gross hypercapnia should occur only rarely during anaesthesia, either as a result of accidental administration of carbon dioxide or due to faulty or unsuitable apparatus.

Whatever the cause, gross hypercapnia presents a unique stress to the homeostatic mechanisms of the intact animal, and survival in the face of this stress depends on the conditions under which it is produced. The modification of autonomic response to hypercapnia by the action of many anaesthetic agents makes it difficult to predict the outcome of such a stress, except under the conditions specified by the few reports of gross hypercapnia in the literature. The recognition of the condition may be extremely difficult, and precise definition depends on the demonstration of elevated levels of carbon dioxide content or tension in the blood.

We do not consider that the development of ventricular fibrillation described by Brown and Miller (1952) has been fully substantiated, although this contention would be difficult to prove during human anaesthesia. We believe that the dangers of rapid reduction of Pco₂ have been overstressed, and that they may present less hazard to the patient than the maintenance of the status quo. It would seem appropriate to draw attention to a statement by Peters and Van Slyke (1931) to the effect that “carbon dioxide excess is unlikely of itself to be of dangerous or even serious significance”. Whilst this statement has been supported by much of the subsequent evidence based on animal experimentation, the condition of gross hypercapnia continues to present the anaesthetist with a source of considerable anxiety.

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REFERENCES


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HYPERCAPNIE ACCIDENTELLE SEVERE AU COURS DE L'ANESTHESIE: RAPPORT D'UN CAS ET REVUE DE QUELQUES EFFETS PHYSIOLOGIQUES

SOMMAIRE

Présentation d'un cas d'hypercapnie grave survenue au cours de l'anesthésie avec description de l'évolution, du diagnostic et du traitement de cet accident. L'hypercapnie était causée par une forte concentration de dioxyde de carbone dans le gaz inspiré après ouverture accidentelle de la soupape de contrôle pour le dioxyde de carbone. Certaines dispositions structurelles de l'appareil d'anesthésie facilitèrent cette méprise et la construction du rotamètre était telle que la bobine était cachée au sommet du tube. Le diagnostic de l'accident décrit aurait été difficile sans analyse de sang artériel. Le malade ne parut pas souffrir particulièrement sous l'effet de cet incident ni de son traitement rapide par l'élimination du dioxyde de carbone du mélangage gazeux inspiré. L'étiole et les effets d'une importante hypercapnie en cours d'anesthésie ont été discutés et une attention particulière a été prêtée au problème de la détermination des anomalies de l'équilibre acido-gazeux.

AKZIDENTIELLE SCHwere HYPERKAPNIE WAHRHEND DER NARKOSE: BESPRECHUNG EINES FALLES UNTER BERÜcksICHTIGUNG EINIGER PHYSIOLOGISCHER EFFEKTEn

ZUSAMMENFASSUNG