THE RELAXANTS AND PULMONARY VENTILATION

BY

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THE INFLUENCE OF RELAXANTS ON PULMONARY VENTILATION

In health the arterial blood carbon dioxide tension (P_{a\text{CO}_2}) of the resting subject is kept constant between about 36 and 44 mm Hg and the arterial pH also shows little variation (pH 7.36 to 7.44). All the techniques used in general anaesthesia tend to cause variations from these normal limits and techniques involving the use of the relaxants are no exception to this rule.

The relaxants reduce ventilation by their action at the neuromuscular junction, reducing the effective response of the muscles to stimuli originating in the central nervous system. These effects on ventilation are additive to those of drugs acting on the respiratory centre.

When an anaesthetized patient is breathing spontaneously some degree of respiratory acidosis is to be expected in anything except the lightest anaesthesia, the P_{a\text{CO}_2} rising and the blood pH falling. Similarly the use of the relaxant drugs in doses sufficient to give a useful degree of muscular relaxation is likely to lead to respiratory acidosis when the patient is breathing spontaneously. A mild degree of respiratory acidosis (P_{a\text{CO}_2} up to 70 or 80 mm Hg) is quite compatible with safe anaesthesia, but the use of the relaxant drugs to produce relaxation for, say, upper abdominal operations is attended by the risk of gross hypercarbia and anoxia. To obviate these dangers it was at one time common to assist respiration when these drugs were used, that is to squeeze the reservoir bag synchronously with the patient's inspiration (Gray and Halton, 1946). Later work, however, suggested that it was desirable completely to abolish spontaneous respiratory activity and to establish fully controlled ventilation. Not only did this make adequate elimination of carbon dioxide more certain; it also contributed in some way to the anaesthesia by itself reducing movement in response to surgical stimulation (Gray and Rees, 1952). This line of thought was carried a stage further by Geddes and Gray (1959) who described the use of passive pulmonary hyperventilation as a flexible adjuvant to anaesthesia. This, however, is a procedure not accepted by all authorities (Clutton-Brock, 1957; Hewer, 1959; Sugita and Davies, 1960).

The Radford nomogram (Radford, 1955; see also Mushin, Rendell-Baker and Thompson, 1959; Nunn, 1960) was designed as a guide to the pulmonary ventilation required to give an alveolar carbon dioxide tension of 40 mm Hg. It was not expressly directed towards anaesthetized patients. For a given rate of ventilation a basal value is read off the nomogram (this is different for males and females) and certain corrections (as, for example, for endotracheal intubation and pyrexia) are applied when relevant. Nunn (1960) has shown that, by a surprising coincidence, the Radford nomogram does, in fact, give a reasonably good guide to the ventilation required to produce an arterial blood carbon dioxide tension of around 40 mm Hg in patients undergoing controlled ventilation during anaesthesia, though the nomogram is of little use when applied to patients breathing spontaneously. The reason for this coincidence is that the figures used by Radford in constructing the nomogram for the production of carbon dioxide by the body are too high for anaesthetized patients and the value he took for the deadspace is too low when it is the arterial carbon dioxide tension which is being considered. These two factors tend to cancel each other out.

This work is of great interest and value, but it has grave limitations in clinical practice. In the first place, as has been pointed out, the nomogram cannot be used in the patient who is breathing spontaneously. To use it as a guide in controlled ventilation a mechanical ventilator is obligatory, since it is not possible to follow a precise pattern of ventilation when using manual pressure on the reservoir bag.

Even in the case of controlled ventilation with a mechanical ventilator there are serious practical
difficulties. Among the most important of these is the fact that the nomogram is based on the assumption that the inspired carbon dioxide tension is zero. This desirable objective is not always achieved when soda lime is used, especially if the flow of fresh gases is kept low. Another obvious source of error is the fact that valves on circle absorbers not infrequently "stick".

When considering the measurement of the volume used to ventilate the patient's lungs it must be remembered that the rubber tubing used in most anaesthetic circuits may expand when gas is pumped into the circuit (Mushin, Rendell-Baker and Thompson, 1959) and that this may invalidate the measurement of ventilatory volume provided on such ventilators as, for example, the Blease pulmoflator. Lastly it goes without saying that the nomogram cannot be applied when the patient is "fighting against the pump" (Comroe et al., 1962).

Clinical anaesthesia is far from being an exact physiological science. Most of the errors which may arise in the assessment of ventilation tend to cause a respiratory acidosis. It is prudent, therefore, for ordinary clinical purposes, to aim at producing a respiratory alkalosis, even when it is not intended to use passive pulmonary hyperventilation as an adjuvant to anaesthesia.

THE INFLUENCE OF PULMONARY VENTILATION ON THE ACTION OF RELAXANTS

When the relaxants are administered and the patient is breathing spontaneously there is likely to be some depression of pulmonary ventilation; on the other hand, when the anaesthetist assumes the responsibility for pulmonary ventilation he is very likely either to overventilate or to underventilate. It is the exception rather than the rule for the PaCO₂ and the arterial blood pH to be within what are regarded as the normal limits for resting subjects under these circumstances.

There is a strong clinical impression that, when light anaesthesia is used together with large doses of the relaxant drugs, passive pulmonary hyperventilation tends not only to ablate spontaneous respiratory effort but also to diminish or ablate response to surgical stimulation. It is tempting to attribute this state of quiescence which hyperventilation produces to an effect at the neuromuscular junction and to deduce that hyperventilation causes a potentiation of such drugs as d-tubocurarine, gallamine and suxamethonium.

There is, however, an alternative explanation. Hyperventilation produces a marked depression of cerebral function and analgesia in the conscious patient (Kety and Schmidt, 1946; Balke, Ellis and Wells, 1958; Clutton-Brock, 1957; Robinson and Gray, 1961). The effect of hyperventilation might thus be due to a central action, an action similar to that of the general anaesthetic agents.

Indeed it is not impossible that pulmonary hyper-ventilation diminishes and does not in fact potentiate the action of the relaxants. There has been, as yet, no work published on this subject in the human. Payne (1958), however, found that carbon dioxide diminished the neuromuscular blocking action of gallamine, suxamethonium and decamethonium in the cat, but increased the action of d-tubocurarine. In a later paper Payne (1960) showed that the action of d-tubocurarine was weakened when the pH of the blood was lowered by the intravenous infusion of acid, a finding which led the author originally to conclude that there must be a specific action of carbon dioxide on the drug.

It is, of course, unwise to apply this interesting work directly to the human patient. Indeed it might well be argued that if there is such a robust difference between d-tubocurarine and the other relaxants in common use some evidence of this might be expected in clinical practice.

There are good theoretical reasons for supposing that the hydrogen ion concentration of the blood and body fluids should influence the distribution of the relaxants and their action at the motor endplate. Suxamethonium is an obvious example since it is largely destroyed by enzymic action and the enzyme primarily concerned is sensitive to changes in pH. There are also reasons of a more general nature. For example, there is evidence that d-tubocurarine is bound to the plasma protein (Aladjemoff, Dickstein and Shafrir, 1958) and such binding will also be influenced by changes in pH (Goldstein, 1949). The relaxants appear to unite with receptor substances situated not only at the neuromuscular junction (Waser and Luthi, 1956) but also probably elsewhere (Chagas, 1962). The union of the drug with its receptor would seem to be, at least primarily, ionic in nature. In considering the effect of pH on the drug-receptor
union not only the effect of pH on the drug molecule must be considered (which in the case, for example, of d-tubocurarine is small over the biological range) but also on the receptor substance as well (Albert, 1952).

This subject offers almost limitless scope for speculation. In summary it can be said that little is known of the relative importance of changes in blood pH on the central nervous system and on the action of the relaxant. This is an important unsolved problem.

THE INITIATION OF SPONTANEOUS RESPIRATION AFTER CONTROLLED VENTILATION

The mere reversal of a relaxant by an antidote is not necessarily sufficient to cause resumption of spontaneous respiratory activity even under the lightest forms of general anaesthesia. This fact is illustrated in figure 1. The patient, a woman of 35 years weighing 73 kg, was anaesthetized for a simple mastectomy. She had been premedicated with promethazine 25 mg and atropine 0.6 mg, given an hour before operation. Anaesthesia was induced with thiopentone (200 mg) and this was followed by 40 mg of d-tubocurarine chloride. Endotracheal intubation was effected without the application of topical analgesic to the larynx and artificial pulmonary ventilation was instituted, an Aintree ventilator being employed, using a fresh gas flow of 9 litres (2.5 litres oxygen: 6.5 litres nitrous oxide) per min. Pulmonary ventilation was adjusted to give an appreciable degree of respiratory alkalosis.

When the operation was completed the patient was taken into a quiet anaesthetic room; positive pressure ventilation was continued as before. Atropine 1.2 mg was administered and this was followed immediately by neostigmine 5 mg. The \( P_a \) rose after the neostigmine had been given, presumably due to a decrease in compliance following the return of muscle tone. Spontaneous respiration, however, did not return. After 20 minutes the nitrous oxide was turned off and pulmonary ventilation was continued with oxygen only (9 litres). Still there was no return of spontaneous

![Diagram](https://academic.oup.com/bja/article-abstract/35/9/521/278127)

**FIG. 1**

Patient given d-tubocurarine. Artificial ventilation continued after the neostigmine was given and later the nitrous oxide was turned off. Spontaneous respiration only restarted after deflation of the cuff of the endotracheal tube.
The fact that respiration may be resumed even when the patient is still in a state of respiratory alkalosis has an important bearing on the safe use of neostigmine, since Riding and Robinson (1961) have shown that the administration of neostigmine to patients in a state of respiratory acidosis is more likely to lead to bradycardia and arrhythmia than when there is a state of respiratory alkalosis. It is therefore unnecessary and perhaps unwise to seek signs of returning spontaneous respiration by reducing the pulmonary ventilation or by adding carbon dioxide to the inspired gas mixture before neostigmine is given.

Fink (1961) emphasized the importance of consciousness in the process of the initiation of respiration after passive pulmonary hyperventilation, concluding that there was a powerful stimulus to respiration depending on the "wakefulness activity of the brain". He found that respiration was resumed in the presence of a low blood carbon dioxide tension when the patient was awake, but not when the patient was asleep. In the series of patients to which reference has been made, however, respiration started when the patient was unconscious and when the carbon dioxide tension was low. The stimulation of afferent nerves in the trachea and pharynx was obviously of great importance in the initiation of spontaneous respiration.

The conflict between these two reports is probably more apparent than real. It is well known that many factors influence spontaneous respiration, a point that has been stressed and elaborated by Gray (1946). It is not surprising that two workers, using quite different experimental conditions, should get quite different results. It can, however, be said that deep anaesthesia, depression of the central nervous system by narcotic drugs, and the application of local anaesthetic solutions to the larynx will make the prompt return of respiration after controlled ventilation more problematical.

**THE USE OF RELAXANTS IN ANAESTHESIA FOR THE "RESPIRATORY CRIPPLE"**

The term "respiratory cripple" is a convenient way of describing a patient who has altered pulmonary function of such severity as to give rise to distressing symptoms and to gross limitation of what can be regarded as normal activity for the patient's age. This is not infrequently associated
with a raised $P_{aCO_2}$ and is usually associated with some degree of cardiovascular disease. The commonest causes are chronic bronchitis and/or chronic hypertrophic emphysema. There is little recorded in the literature about anaesthesia for this type of patient, but it seems that there is a general reluctance to anaesthetize such patients with techniques involving the use of the relaxant drugs and positive pressure ventilation. This reluctance seems to be due to two main factors. Firstly, there is the fear that carbon dioxide will be so efficiently “washed out” of the body that spontaneous respiration will not readily reappear at the end of operation. Secondly, there is the opposite fear that, after the relaxants have been given, the anaesthetist will not be able to provide adequate pulmonary ventilation and that bronchospasm and trapping will result in hypoxia and hypercarbia.

Utting, Gray and Rees (1962) investigated ten such patients with respiratory acidosis who were presented for routine surgery. In four of these patients pre-operative medical treatment (postural coughing, antibiotics, etc.) was considered practicable and desirable. Premedication was with promethazine and atropine and the anaesthetic technique used did not differ from that described previously. A deliberate attempt was made to hyperventilate the patients’ lungs during the anaesthetic. A Boyle Mark II circle absorber was used with a fresh gas flow of 4 l./min. The minute volumes were between 15 and 30 l./min delivered at rates between 30 and 60/min. It must, however, be emphasized that this was not the maximum ventilation which could have been achieved.

Table I shows the pre-operative values for the carbon dioxide tensions obtained from arterialized venous blood after the method described by Brooks and Wynn (1959). Spot values are shown for the carbon dioxide tensions obtained during the course of the anaesthetic. It can be seen that a relative or absolute respiratory alkalosis was achieved in every case. Table II shows the carbon dioxide tension of the blood before operation of those patients who had a respiratory acidosis and contrasts it with that when spontaneous respiration seemed to have been re-established. From Utting, Gray and Rees (1962).

### Table I

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Duration of anaesthesia (hours)</th>
<th>$P_{CO_2}$ values (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td>Emphysema</td>
<td>2</td>
<td>55</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1</td>
<td>44</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Pre-operative $P_{CO_2}$ values (mm Hg)</th>
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<tbody>
<tr>
<td>Initiation of respiration</td>
</tr>
<tr>
<td>34</td>
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<tr>
<td>55</td>
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<tr>
<td>34</td>
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<td>59</td>
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<td>48</td>
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<td>56</td>
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It can be seen that some respiratory effort occurred when the carbon dioxide tension was still quite low, and that there is a remarkable similarity between the tension at which respiration became established and that found in the ward before anaesthesia was commenced. It must be emphasized that it is unlikely that these results would have been obtained if powerful depressant drugs had been used in the premedication or if the patients had been subjected to deeper anaesthesia.
PROLONGED APNOEA AND HYPOPNOEA AFTER THE USE OF RELAXANTS

There is no shortage of accounts of postoperative apnoea and hypopnoea after the use of the relaxants. Indeed this is one of the subjects on which anaesthetic workers have tended to be most prolix. Investigations on the cases which have been recorded, however, have usually been very incomplete and this is hardly surprising since they tend to occur at times and in places which militate against full investigation.

Of the relaxant drugs in common clinical use both suxamethonium and gallamine have special pharmacological features which may contribute to, or cause, prolonged hypopnoea or apnoea. In the case of suxamethonium, a deficiency of, or the presence of an atypical form of, pseudocholinesterase may be the cause. In the case of gallamine, renal insufficiency may result in delayed excretion and so recovery. d-Tubocurarine and gallamine, moreover, will cause prolonged apnoea in patients with frank (or "latent") myasthenia gravis.

There remains, however, a group of patients in which these causes do not seem to operate. Hunter (1956) described six cases of prolonged apnoea which terminated fatally and which occurred in elderly, dilapidated patients who, although ill, were not expected to die. This report was followed by a voluminous correspondence in the medical journals from which two facts emerged. First, there was no doubt that Hunter had described a real condition and, secondly, there was no unanimity about its aetiology. Usually in the cases described there was either a history of intestinal obstruction or of pulmonary dysfunction, but some cases did not fit into either category. Theories abounded to explain this occurrence. The condition was said to be due to too heavy premedication, the use of d-tubocurarine with suxamethonium, the use of suxamethonium, the use of d-tubocurarine, the use of too much neostigmine, the use of too little neostigmine, positive pressure ventilation, low level of cholinesterase, hypokalaemia, etc.

Much of what has been written on this subject

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**Fig. 3**

A diagrammatic representation of some of the causes of prolonged hypopnoea after d-tubocurarine. From Utting and Gray (1962b).
has been determined by the conception that postoperative apnoea is a single entity (like measles) and that the anaesthetist has to seek a sovereign remedy. More recently, however, it has been increasingly realized that the condition has many causes. The syndrome of tracheal tug, "miniature" respirations, cyanosis when breathing air and unconsciousness is entirely nonspecific. It presents a diagnostic problem to the anaesthetist in much the same way as abdominal pain may present a diagnostic problem to the surgeon, or nystagmus to the physician.

The multiple causation of prolonged apnoea and hypopnoea has been emphasized by, for example, Paton (1958), Gray, Dundee and Riding (1958) and Churchill-Davidson and Wise (1960). Recently Brooks and Feldman (1962) have made a valuable contribution by suggesting that metabolic acidosis may be one important aetiological factor. Another important factor is hypercarbia, which may develop insidiously and with ease in the very ill patients and be exacerbated during ill-advised attempts to restart spontaneous respiration; it has been recognized as one very important cause of postoperative hypopnoea. Some of the main causes of this syndrome as found by Gray, Dundee and Riding (1958) and Uting and Gray (1962b) have been included in figure 3.

REFERENCES


