INADEQUATE POSTANESTHETIC VENTILATION
Curare, Anesthetic, Narcotic, Diffusion Hypoxia

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Inadequate respiratory exchange in the immediate postoperative period is a frequent occurrence, especially after certain types of surgery such as thoracotomies and upper abdominal operations. In the majority of cases, however, the condition gives no clinical symptoms and thus passes unnoticed unless measurements are made of arterial oxygen saturation and $F_{\text{EO}_{2}}$.

Several factors may contribute to this respiratory insufficiency: depressant effect of anesthetics and/or narcotics, residual effect of neuromuscular blocking agents, depressant effect of high carbon dioxide tension on the respiratory center, anoxic brain damage, paralysis of intercostal muscles caused by spinal or epidural analgesia, wound pain, reduction of large incisional herniae, or the application of tight dressings around the abdomen and lower part of the thorax. Following resections of lung tissue, the residual number of functioning alveoli may be too small to allow an adequate exchange of gases, and paradoxical movements of the chest wall after thoracoplasty may severely hamper respiratory exchange. In neurosurgery, insufficient respiration may be caused by a raised intracranial pressure. Pre-existing disease such as pulmonary emphysema, kyphoscoliosis, or poliomyelitis may further increase the degree of respiratory insufficiency.

In the following, only conditions caused by muscle relaxants, by anesthetic agents and narcotics, and by diffusion hypoxia, will be considered.

Some confusion arises from the fact that different authors use different definitions for the terms dealing with adequacy or inadequacy of respiration.

Woolmer defines insufficient respiration as a condition where gas exchange between the lungs and the blood falls below that between the tissue and the blood, i.e., external respiration cannot keep pace with internal respiration.

This definition corresponds to the term asphyxia. Bihlemann defines asphyxia as a condition which, if not corrected, will lead to death within a short time because of increasing hypoxia and hypercapnia, whereas in his terminology respiratory insufficiency is a condition where an equilibrium exists between external and internal respiration at an abnormal level with decreased arterial oxygen saturation and elevated carbon dioxide tension.

In Scandinavia, the term asphyxia denotes conditions with decreased arterial oxygen saturation and elevated carbon dioxide tension irrespectively of whether a steady state exists or not.

In Anglo-Saxon literature the term apnea indicates a condition where for some reason respiratory movements do not take place. Strictly speaking, it means cessation of breathing caused by hypoxemia, but the term now seems to be universally adopted to denote other conditions of respiratory standstill as well, and misunderstandings due to this extended use of the word are rare.

THE MUSCLE RELAXANTS

Today the most common cause of postoperative respiratory inadequacy is the use and misuse of muscle relaxant drugs. In this connection, the technique with which they are used plays a major role for the incidence of prolonged apnea or respiratory insufficiency.

Folkes advocates the use of assisted rather than controlled respiration: "It can be stated . . . that with careful technique adequate muscular relaxation and respiratory exchange can be maintained with assisted respiration. Unquestionably the greatest danger in using muscle relaxants is prolonged and, on occasion, irreversible apnea, which has been reported most frequently after the use of depolarizing relaxants. The only sure way to avoid postoperative apnea is to abstain from
producing apnea during surgery. Guadagni is of the same opinion.

Gray and Rees regard apnea as an important feature of the technique of anesthesia in major surgery. They warmly advocate the use of controlled respiration, stating that less amounts of anesthetics and of relaxants are needed and that hyperventilation has a protective effect against reflex responses to surgical, in particular intraperitoneal, trauma. In addition, hyperventilation produces electroencephalographic signs of deeper narcosis under very light anesthesia. This opinion is shared by Clutton-Brock and Dundee.

Several methods have been suggested to evaluate the adequacy of respiration in the postoperative period. Most of these methods, however, are too complicated and time-consuming for routine use and have not gained wide popularity.

Hamilton used the end-expiratory carbon dioxide concentration as an indicator. Linderholm and Norlander measured arterial carbon dioxide tension. In the opinion of Hood and associates, alveolar ventilation is the most important measurement when evaluating adequacy of respiration. They recorded tidal volume and respiratory rate, using the normal values for anatomical dead space given by Fowler.

Guadagni is of the opinion that "the danger point may be considered passed when the patient is able to satisfy his oxygen requirements for more than five minutes while breathing room air in as much as he can be sent safely to the recovery room to have oxygen administered by catheter, mask or tent."

In the authors' opinion, the "head-lift" test is a valuable sign of returning muscle power. The test is based upon the observation that the muscles of the neck are among the first to be influenced by the paralyzing action of muscle relaxants as shown by the fact that conscious subjects, when given small doses of curare which do not cause respiratory embarrassment, are often unable to lift the head from the pillow by flexing the neck (whereas they may well be able to do so by stiffening the back). We have employed the test for several years to the extent that no patient is moved from the operating table until he has lifted his head in the manner described, and in emergency cases the endotracheal tube is left in place until that moment. If the test is negative, controlled respiration is resumed regardless of whether the patient's own respiration appears adequate or not.

We have been pleased with the method since so far we have not seen failures, i.e., when the test is positive, "re-curarization" does not occur, and we therefore tend to disregard the fact that a number of patients are probably ventilated somewhat longer than strictly necessary.

Following 10,829 major operations where succinylcholine and d-tubocurarine had been used on alternate days for relaxation we found, using the above mentioned criteria, insufficient respiration in 2.3 per cent of cases after succinylcholine and in 1.4 per cent after d-tubocurarine. In the majority of cases the duration was between 15 and 30 minutes (and this group also includes patients who were still under the influence of the anesthetic at the end of operation), but in a few cases the respiratory insufficiency was prolonged, up to seven hours. Irreversible curarization did not occur.

When prolonged apnea occurs as a result of overdose or bad timing of relaxants, the diagnosis is most often easy and can be established after one look at the anesthesia record, but in some cases other factors are in operation, and diagnostic difficulties may arise.

Hypocapnia following hyperventilation is an obvious cause of postoperative apnea, but occasionally the true cause is hypcapnia in combination with the effects of the anesthetic agents. Clinically it may be impossible to distinguish between the two conditions, and if doubt exists it is better to assume the latter possibility and to treat the patient with hyperventilation for fifteen minutes followed by hypoventilation with oxygen for two minutes. In either case, spontaneous respiration will often recur at the end of this procedure.

The Hering-Breuer reflex is stimulated by rhythmical inflation of the lungs, and after an operation where controlled respiration has been employed a state of "habit apnea" may exist. Guadagni advocates irregular compression of the anesthesia bag where this condition is suspected.

The most logical way to differentiate be-
tween neuromuscular block and apnea from other causes is electrical stimulation of a peripheral nerve such as the ulnar nerve.²

To avoid prolonged neuromuscular block when using d-tubocurarine to patients in apparently good condition, Gray and Halton ¹⁵ advocated the intravenous administration of a test dose. After 5 or 6 mg. of the drug prior to induction of anesthesia, the ordinary response is slight paresis of the ocular muscles, but occasionally more severe reactions are seen, even complete paralysis with apnea. The present authors have been using the test dose for several years and regard it as a useful guide to subsequent dosage of relaxant. Also, some subclinical cases of myasthenia gravis have been diagnosed.¹⁶

Excessively prolonged apnea following a single dose of succinylcholine has been reported by several authors,¹⁷,¹⁸ but the incidence of this complication is low, in the experience of the authors about 1 in 20,000 cases.

Under normal conditions, a fairly reliable guide to the patient's reaction can be obtained by noting the time from the injection of the dose for endotracheal intubation (usually 40 to 60 mg.) until spontaneous respiration returns.

Prolonged succinylcholine apnea may be seen in patients suffering from hepatic disease with decreased plasma cholinesterase activity, but provided no acidosis is present, alkaline hydrolysis will eventually terminate the block.⁴

Tachyphylaxis against succinylcholine is likewise infrequent, but when it does occur it is a disturbing complication. Large amounts of succinylcholine are likely to be given before the true nature of the condition is realized, and a prolonged neuromuscular block may be expected because of accumulation of succinylmonocholine. This substance, in addition to a blocking effect of its own, will also depress the break down of succinylcholine, especially in patients whose urinary secretion is depressed.⁴

If tachyphylaxis to succinylcholine develops during the course of an anesthetic it is probably better to discontinue the administration of relaxants and to produce adequate muscular relaxation by means of general anesthesia alone, although Foldes et al.¹⁹ find that under such circumstances, a small dose of a non-depolarizing muscle relaxant will give excellent relaxation for a long time, and that the resulting neuromuscular block is easily antagonized by neostigmine. This phenomenon is explained by a change from the depolarizing into a non-depolarizing block after prolonged administration of succinylcholine.

If both depolarizing and non-depolarizing drugs are given to the same patient, prolonged apnea may occur. The use of succinylcholine to facilitate endotracheal intubation followed by a non-depolarizing agent when the patient has regained his full respiration is probably a safe practice although the present authors fail to see any particular advantage in the method. If, however, succinylcholine is given to a curarized patient at the end of an operation to allow closure of the peritoneum, prolonged respiratory depression is more likely to result.

That temperature influences the duration of neuromuscular block has been shown by Zalmis and co-workers.⁵⁰,⁵¹ Woolman and Cannard ²² found that during intrathoracic procedures the muscle temperature could decrease enough to cause a prolonged and intensified effect of depolarizing agents, and advocated monitoring the esophageal temperature in cases where extraordinary heat loss is likely. In case of prolonged apnea from this cause, rewarming is of course the appropriate treatment.

Certain antibiotics may produce neuromuscular block and may intensify the effect of previously injected muscle relaxants. Reports have appeared describing apnea and even death following the intraperitoneal injection of neomycin.⁵³,⁵⁵ Pittinger et al.²⁸ found that neomycin produced a neuromuscular block which was potentiated by ether and antagonized by neostigmine, and studies by Brazil and Corrado ²⁷ showed that streptomycin had similar effects.

**Central Effects**

Although the main effect of the relaxant drugs is a peripheral one, there is some evidence that a central action may take place. Ellis and co-workers ²⁳ produced apnea by
means of large doses of decamethonium and \(d\)-tubocurarine in cats and dogs anesthetized with pentobarbital. In the period during which electrical stimulation of the phrenic nerve caused a diaphragmatic contraction, but where spontaneous respiration and phrenic nerve action potentials were absent, they found that the administration of a central respiratory stimulant caused an instantaneous resumption of respiratory activity.

Hunter\(^{22}\) similarly found that in patients with respiratory depression caused by a depolarizing agent, nikethamide could for a short time augment respiration and cough reflex.

During neurosurgical interventions, Consoled\(^{20}\) stimulated anterior spinal nerve roots and found muscle contraction although the patients had received apneic doses of decamethonium.

In 1953, Dripps\(^{21}\) showed that electro-phrenic stimulation could provoke diaphragmatic contractions in patients 15 to 20 minutes before termination of apnea caused by decamethonium.

"Irreversible Curarization"

Several reports have appeared in the literature describing so-called irreversible or nestigmine resistant curarization.

The clinical pictures of patients in whom this complication has occurred have shown certain similarities being elderly patients suffering from ileus or perforitis of long duration with subsequent dehydration and electrolyte derangement, and the pre-operative fluid and electrolyte therapy has most often been inadequate.

Foster\(^{22}\) found two general features in these patients: an apparent resistance to muscle relaxants during induction of anesthesia and respiratory depression and unconsciousness after the operation. He hypothesized an abnormal penetration of the relaxants into the central nervous system because of potassium deficiency.

Hunter\(^{23}\) described six similar cases, all of which ended fatally. In two of his cases, treatment with potassium solution was attempted, but the effect was only temporary, and these two patients also died. He advocated the use of succinylcholine in such cases.

Gray et al.\(^{24}\) state that in the above mentioned type of patients all muscle relaxants are contraindicated.

The authors have been using muscle relaxants for such cases for years and believe that they are of great help in the anesthetic management. These very ill patients seem to tolerate deep planes of general anesthesia poorly, and a considerable degree of relaxation of the abdominal wall is often desirable from a surgical point of view. In the study previously referred to,\(^{11}\) we saw two cases of excessively prolonged neuromuscular block, lasting seven hours each. One case followed the administration of \(d\)-tubocurarine, the other succinylcholine. Both cases occurred in the beginning of the study (which was undertaken in 1954), but after some light had been shed on the etiology, no further cases occurred. We therefore feel justified in expressing the opinion that when proper precautions are taken as outlined below muscle relaxants can be safely given to the patients in question.

Prior to operation, one or more hours are spent with restorative measures. Fluids and electrolytes, including potassium, are given intravenously, and since hypovolemia is invariably present, blood or plasma is administered. Oxygen therapy by nasopharyngeal catheter is a routine because, as Cullen\(^{11}\) points out, "hypoxia is a potent factor in the initiation or perpetuation of shock." A complete correction of the fluid and electrolyte derangement is not practical within the time usually available, but the treatment is continued during and after operation.

The cases are handled by senior anesthetists. Cyclopropane is our agent of choice, and a fairly light level of anesthesia is maintained. Muscle relaxants are given as needed.

After the operation the endotracheal tube is left in place with the cuff inflated until the "head-lift" test is positive, and great care is taken to avoid hypoxia during this period.

Using these principles we have found that, should prolonged curarization occur, it is of short duration, and the outcome will not be fatal.

Anesthetics and Narcotics

The respiratory depression associated with deeper planes of inhalation anesthesia rarely
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extends into the postanesthetic period due to the rapid elimination of these agents. Dripps in 1947 found a rapid decrease in arterial carbon dioxide tension within the first three to seventeen minutes after discontinuation of cyclopropane anesthesia. Hamilton found that of 13 patients who had received a narcotic prior to cyclopropane anesthesia, 4 had elevation of PaCO2 on arrival in the recovery room, whereas carbon dioxide tension was normal in 11 patients who had received cyclopropane without opiate. Following ether anesthesia, no increase in carbon dioxide tension was found. Linderholm and Norlander reported similar findings.

Much attention has been directed towards the respiratory depressant properties of thiopental. These were realized shortly after the induction of the agent and the work of Brodie and co-workers clearly showed that the drug accumulated in fatty tissues and that elimination was a slow process.

Studying the respiratory effects of thiopental, Patrick and Faulmer found that ventilation decreased progressively as the depth of anesthesia increased. When 5 percent carbon dioxide was inhaled, a marked increase in ventilation occurred in lighter planes of anesthesia, whereas in deeper planes the response was less pronounced.

In 1947, Neff et al. advocated the addition of meperidine to the combination thiopental-nitrous oxide. Their favorable results were confirmed by Bratman and Cullen and the method soon gained world-wide popularity.

Although the depressant effect upon respiration of opiates had been known for a long time, early studies on meperidine seemed to indicate that the respiratory depression seen after this drug was transient and slight. Later studies showed, however, that in equipotent analgesic dosage, meperidine depressed respiration as much as morphine and measurements in the recovery room have demonstrated that a certain degree of respiratory acidosis frequently exists when this type of anesthesia has been used.

The work of Eckenhoff and associates have clarified the significance of the individual components in this combination of drugs. These authors showed that thiopental, when given alone, caused only minimal respiratory depression in doses commonly employed, but when opiates were added, a considerable degree of depression was always seen. Their studies also confirmed the statement by Loeschke et al. that it is not possible to evaluate respiratory depression by simple measurements of respiratory rate and tidal volume. Determinations of arterial or alveolar carbon dioxide content, or recording of the ventilatory response to carbon dioxide, are necessary for the full appreciation of the condition. In their conclusion that narcotics should be omitted not only when weaker respiratory depressants are studied, but also in clinical practice unless a definite indication for their use exists, they are in agreement with the view expressed by Cohen and Beecher.

The hazards of opiate administration to patients emerging from general anesthesia have been stressed by Eckenhoff et al. and by Dripps and associates. Severe depression of respiration and even apnea may follow such injections.

Under normal clinical conditions, the respiratory depression following the administration of thiopental-meperidine-nitrous oxide anesthesia is not of such proportions as to arouse the concern of the anesthesiologist. On some occasions, however, a more profound depression is seen, and in such cases the use of an opiate antagonist may be considered.

THE OPIATE ANTAGONIST

The early literature on the use of N-allylnormorphine was reviewed in 1955 by Huggins and Moyer. They confirmed earlier findings that nalorphine is a depressant drug in itself, and they also showed that when only moderate doses of opiates had been given, the antagonistic effect was slight, and was accompanied by prominent side effects such as nausea, dizziness, sweating, and hallucinations. These findings correspond to those of Lasagna and Beecher who demonstrated that the combination of 2 mg. of nalorphine and 10 mg. of morphine produced analgesia and side effects indistinguishable from those obtained with 10 mg. of morphine, and similar results were found with the combination of 5 mg. of nalorphine and 15 mg. of morphine.

A second opiate antagonist, levallorphan,
was introduced in 1952 and was given clinical trial by Hamilton and Cullen in 1953. These authors demonstrated that levorphanol was able to reverse respiratory depression seen after various opiates, and when given prior to the opiate, it protected against respiratory depression. In subsequent works, Cullen and Santos injected levorphanol and levallorphan simultaneously in ratios of 4:1 and 10:1. While they found severe side effects with the higher dose of levorphanol, the lower dose did not seem to increase the number of untoward reactions normally seen after levorphan alone, and the protective effect on respiration was good. They, therefore, suggested that a mixture of opiate and antagonist might be found which would prove useful in clinical practice.

Megirian et al. combined levorphanol with alphaprodine and were able to find a ratio at which no respiratory depression was found.

Eckenhoff and associates were unable to confirm these findings and found no effect of levorphanol when injected together with levorphan in 1:10 or 1:1 ratios, and they, therefore, concluded that the antagonists are only effective when opiate depression already exists.

The introduction of amiphenazole (Dapta-zole) by Shaw and associates was followed by a series of favorable reports. According to these, amiphenazole could effectively counteract the undesirable side effects of morphine without affecting pain relief, and in contrast to the two other antagonists, no side effects were seen.

A controlled study by Fraser et al. did not confirm this. Using mixtures of morphine and amiphenazole and of morphine and saline, no differences in effects or side effects could be observed. They noted, however, that the doses of morphine, with or without amiphenazole, could be rapidly increased to very high levels without respiratory depression.

Eckenhoff and Norton were also unable to demonstrate any antagonism to morphine by amiphenazole. They did find, however, that the psyche in some of the patients improved notably when amiphenazole was given.

From the available data it may be concluded that nalorephine and levallorphan are effective in antagonizing respiratory depression caused by large doses of opiates. They are depressant agents in themselves and may increase depression caused by barbiturates.

While they are pharmacologically interesting, their place in the treatment of patients is doubtful. It is the experience of the author from a considerable number of narcotic poisonings seen at the Bispebjerg Hospital Center for treatment of poisoned patients, that supportive therapy alone is successful even in severe cases of narcotic poisoning. One of us (W.D.) has seen a case of fulminant and fatal pulmonary edema following the injection of 15 mg of nalorephine in a young, healthy man poisoned with morphine, and although this complication does not seem to have been encountered by others, it is our belief that the routine use of the drugs in narcotic poisoning is not indicated.

In the treatment of postoperative respiratory depression, our feelings are similar. Since such cases are often of mixed origin, and the drugs may further increase depression caused by barbiturates, we tend to agree with Landmesser and co-workers that "the administration of a narcotic antagonist in the presence of respiratory depression of undetermined etiology is discouraged and condemned except as a diagnostic test in single small therapeutic dosage."

**DIFFUSION HYPOXIA**

Fink et al. and Fink have described a condition of mild hypoxia which may occur at the termination of nitrous oxide-oxygen anesthesia, when the patient is allowed to breathe room air. It is characterized by inadequate oxygenation in spite of adequate ventilation and is explained by the rapid outflow of nitrous oxide from the blood into the lungs at this stage.

The fall in oxygen saturation found in the study averaged 7-9 per cent with a maximum of 10.5 per cent and the condition might last for more than 10 minutes.

In certain cases, such as myocardial disease or following pneumonectomy, the condition may have serious consequence and may even lead to cardiac arrest.

With the commonly used technique, cyclopropane anesthesia followed by nitrous oxide-oxygen during wound closure, diffusion...
hypoaxia is particularly apt to occur, and Fink suggested that this procedure might account for some of the cases of emergence deiurium seen after cyclopropane anesthesia.

Prophylaxis against this type of hypoaxia is the administration of oxygen during the first few minutes following nitrous oxide anesthesia.

CONCLUSION

Inadequate postoperative respiration happens according to the literature rather often. The most common cause seems to be the use of muscle relaxants. Several methods to evaluate this adequacy of respiration have been advocated by different authors. In our opinion a valuable sign of returning muscle power is the "head-lift" test, which has been used for several years to the extent that no patient is moved from the operating table until he can lift the head from the pillow by flexing the neck, with the result that "re-curarization" never has happened.

Much attention has been directed to the respiratory depressant properties of thiopental, but several authors agree that thiopental alone causes only minimal respiratory depression in doses commonly used, but if opiates were added a considerable degree of depression was always seen. We agree with other authors in the opinion, that a routine use of opiate antagonists are not indicated.

A condition of mild hypoaxia which may occur at the termination of nitrous oxide-oxygen anesthesia, when the patient is breathing room air, is discussed and the prophylactic treatment of this type of hypoaxia must be administration of pure oxygen a few minutes after anesthesia with nitrous oxide. The problems around this type of hypoaxia is not quite clear yet and seems to be a point to which more attention should be paid.

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TOXIFERIN The synthetic calabash alkaloid C-Toxiferin I is a long acting non-depolarizing muscle relaxant; it is readily antagonized by anticholinesterases. A strong cumulative effect is seen when the first dose of toxiferin is followed by a second injection or by curare. Effects on circulation and release of histamine are minimal. In conscious volunteers paralysis of swallowing lasted considerably longer than the depression of respiration. The drug should be useful in prolonged operations and in the treatment of tetanus. (Seeger, H.: Curarization with Calabash Alkaloid Toxiferin, Der Anaesthesist 10: 129 (May) 1961.)

CYTOCHROME C The infusion of 10 mg./kg. of a 10 per cent solution of cytochrome C in 15 dogs, rendered acutely anoxic, caused a delay of the appearance of bradycardia and an accelerated return of normal complexes after oxygenation. The anoxic electrocardiographic changes, in contrast, were markedly aggravated by the infusion of cytochrome C. (Vernejoul, E. H., and others: Les Effets du Cytochrome C dans l'Anoxie, Anaesth. Analg. (Par.) 17: 394 (Sept.–Dec.) 1960.)

ACETYLCOLINE The synthesis, storage, and release of acetylcholine were studied in perfused and intact superior cervical ganglia of cats. Of the extractable acetylcholine in a normal ganglion about 85 per cent is available for release by nerve impulse. This must be located in the nerve endings while the remainder is in the intraganglionic portions of the preganglionic axons. The depot acetylcholine exists as two fractions, the smaller of which is more readily available for release. (Birks, R., and MacIntosh, F. C.: Acetylcholine Metabolism of a Sympathetic Ganglion, Canad. J. Biochem. Physiol. 39: 787 (Apr.) 1961.)