ASSESSMENT OF THE EFFECTS OF DRUGS ON RESPIRATION

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Many drugs used in anaesthetic practice such as the opiates, sedatives, barbiturates and volatile anaesthetic agents cause respiratory depression. This often leads to a cautious use of such agents and on occasions this may lead to the administration of a dose of drug which is less than that desired for adequate therapeutic effect. This may often be the case with the administration of opiates for post-operative pain. Consequently, there is a great interest in measuring the respiratory effects of these commonly used drugs both in the laboratory and in the clinical environment, and this interest clearly extends into assessing the efficacy and safety of new compounds and of novel modes of administration of new and conventional agents.

Of prime importance in such studies is the development of suitable methods for assessing the respiratory effects of these drug regimes. The methods must be able not only to quantify the degree of respiratory depression, but also detect alterations in the regulation of breathing which may indicate the potential for serious depression to occur. A number of methods are available which fulfil these requirements to varying degrees in different applications. This paper describes and classifies these methods, indicates the applications in which they are most useful and outlines some recent findings.

MEASUREMENT OF RESTING BREATHING

Ventilation is normally well regulated to ensure blood-gas homeostasis. It is thus of primary importance to investigate the effects of drugs on the regulation of ventilation during resting breathing. Ventilation may be measured or its effectiveness assessed by measurement of blood-gas tensions.

Practical measurement of ventilation

Methods generally involve either (a) direct measurement of ventilation where the subject is required to use a mouthpiece and nose-clip or tight-fitting face mask; or (b) indirect measurements which avoid the use of direct attachment to the airway so as to render breathing more natural, avoid increased deadspace, allow greater subject mobility and facilitate measurements during sleep.

Direct methods. Spirometry: the subject breathes into a spirometer (bell, piston or wedge type), with carbon dioxide absorbed if necessary, the change in spirometer volume being recorded. Inaccurate response at high frequencies may cause errors with rapid breathing.

Pneumotachographs: the pressure difference across the pneumotachograph head is proportional to flow. Electronic integration of the flow signal provides a volume signal which may be summed to give minute volume. Errors may be caused by temperature changes and moistening of the pneumotachograph screen by expired gas or alterations in gas composition.

Other direct methods of measurement of ventilation include mechanical flow meters (e.g. dry gas meters), hot-wire anemometers, turbulent flow resistors and ultrasound devices. A full account of methods of direct measurement of ventilation is given by Nunn (1977).

Indirect methods. Canopy monitor: the subject's head is enclosed in a rigid canopy with the neck sealed with a foam rubber gasket (Sorkin et al., 1980). The canopy is supplied with a fresh gas flow and is maintained at atmospheric pressure by removing gas at a suitable rate. A pneumotachograph or spirometer attached to the canopy measures ventilatory volumes. Restricted access to the patient may be a disadvantage in pharmacological studies, although the method does facilitate measurement during sleep.

Strain gauges: these are applied around the torso and measure changes in circumference during breathing. The mercury-in-silastic strain gauge is the commonest method, and with multiple gauges and electronic signal processing a reasonable estimation may be obtained of tidal volume and of the volumet-
ric contributions of the rib cage and abdomen/diaphragm (Faithful, Jones and Jordan, 1979). The accuracy of these devices is limited because changes in shape of the torso alter the relationship between circumference and volume. Such shape changes may occur at the extremes of lung volumes, when the work of breathing is increased or when changing position.

Electrical impedance pneumography: changes in electrical impedance of the thorax that occur during breathing are measured. The accuracy of this technique is reported to be somewhat limited, especially when changing position (Ashutosh et al., 1974), and it is not clear whether the measurements relate to change in thoracic circumference or volume.

Magnetometry: a coil placed on one body surface generates an electromagnetic field that is sensed by another coil on an opposite surface (Mead et al., 1967). Pairs of coils on the rib cage and abdomen are generally used to measure anteroposterior diameters which are then related to volume changes. Changes in shape of the torso under certain circumstances can produce large errors in volume estimations, although use of multiple magnetometers may overcome this difficulty by enabling suitable calculations of cross-sectional areas.

Respiratory inductive plethysmography: two zig-zag coils of insulated wire attached to highly compliant belts are worn around the rib cage and abdomen. Changes in cross-sectional area of the thoracic or abdominal coil region produce proportional changes in coil self-inductance, which is thus related to change in volume of the appropriate region. Since the transducer measures cross-sectional area directly, virtually independent of shape, the accuracy of volume measurement is little affected by distortion of the thorax or abdomen and a single calibration is valid over a wide range of changes in body position (Cohn et al., 1978; Watson, 1980). This method is therefore highly suited to long-term monitoring and the author and his colleagues have successfully applied it to testing the respiratory effects of drugs (Catling et al., 1980; Jordan, Jones and Pinto, 1980; Royston, Jordan and Jones, 1981). Excessive body movements can produce artefacts in the respiratory signal and care should be taken to ensure that the belts remain in place.

Other indirect methods of measurement of ventilation include body plethysmography (Johnson and Mead, 1963) and the pressure capsule (Wright and Callan, 1980). A thorough review of methods for monitoring ventilation without a physical connection to the airway has been presented by Sackner (1980).

**Practical measurement of blood-gas tensions**

**Direct methods.** Arterial blood samples: sampling of arterial blood and subsequent blood-gas analysis enables $Po2$, $PCO2$ and pH to be measured directly. Repeated arterial punctures or arterial catheterization may be considered unethical procedures for the assessment of drugs in normal subjects and most patients. “Spot” samples may miss transient changes in breathing and the action of taking a sample can disturb the pattern of breathing.

Sampling of arterialized blood: arterialized capillary or superficial venous blood may be sampled to obtain an index of arterial blood-gas tensions. Changes in peripheral circulation may occur as a result of drug administration thereby altering the relationship between peripheral and arterial blood-gas tensions.

**Indirect methods.** Transcutaneous methods: diffusion of oxygen and carbon dioxide through the skin enables the measurement of $Po2$ and $PCO2$ using special electrodes, mass spectrometry or infra-red absorption analysis. The instruments may require initial calibration by checking the subject's arterial blood-gas tensions and the accuracy of measurements can be impaired by changes in skin blood flow and metabolism. Response times are usually of the order of minutes.

End-tidal carbon dioxide sampling: sampling of the end-tidal $PCO2$ is a convenient means of estimating $PCO2$ in arterial blood and is reasonably accurate in patients with normal lungs. Changes in arterial $PCO2$ may therefore be estimated on a breath-by-breath basis by continuous sampling of expired gas with a rapidly responding infra-red carbon dioxide analyser or respiratory mass spectrometer. The relationship between end-tidal $PCO2$ and arterial $PCO2$ can be altered by large changes in respiratory rate or tidal volume.

End-tidal oxygen sampling: the mass spectrometer or fuel cell (Weil, Sodal and Speck, 1967) may be used to sample end-tidal $Po2$. End-tidal $Po2$ is not a reliable index of arterial $Po2$ because of large and variable alveolar–arterial $Po2$ differences.

Ear oximetry: a non-invasive estimation of arterial blood oxygen saturation using ear oximetry is convenient and reasonably accurate. Automatic computations from absorbance of eight different wavelengths of light enable allowances to be made for ear blood volume, skin thickness and pigmenta-
Interpretation of measurements of ventilation and blood-gas tensions

Many pharmacological agents alter oxygen consumption and it is important to remember that minute volume may change in response to metabolic requirements. For example Jennett, Barker and Forrest (1968) found that morphine 10 mg depressed resting ventilation by 20% but also reduced oxygen consumption by 23%. Further, Santiago and colleagues (1979) found that ventilation at different levels of exercise was significantly reduced after morphine 14 mg, but that oxygen consumption during exercise was similarly reduced so that the relationship between ventilation and metabolic rate was not altered. Decreased ventilation does not therefore necessarily indicate that ventilation is depressed and blood-gas estimations are crucial in interpreting changes in ventilation in relation to metabolic requirements. Adequacy of ventilation may be assessed from measurements of arterial P\textsubscript{CO}_2, an increase in P\textsubscript{CO}_2 implying that alveolar ventilation has diminished in relation to carbon dioxide production. Sequential sampling of arterial P\textsubscript{CO}_2 before and after the administration of a drug enables quantitation to be made of the magnitude and time course of any change in ventilation in relation to metabolic requirements.

Measurements of arterial P\textsubscript{O}_2 are generally considered less useful in assessing the effects of drugs on the control of ventilation, since the variable alveolar–arterial P\textsubscript{O}_2 difference reflects the efficiency of gas exchange and is mainly dependent on the relative distribution of pulmonary ventilation and perfusion.

In addition to the effects on minute volume and blood-gas tensions, respiratory depressant drugs often produce marked changes in breathing pattern. The normal regular breathing pattern may become irregular, with variable tidal volumes and occasional apnoeic episodes or sometimes a Cheynes–Stokes pattern with tidal volume waxing and waning. This type of change may be quite pronounced even when overall ventilatory depression is minimal: for example striking changes in breathing pattern were reported after phenoiperidine and morphine even though end-tidal P\textsubscript{CO}_2 was only increased by 0.25–0.4 kPa (Jennett, Barker and Forrest, 1968). It is therefore desirable to include continuous measurements of ventilation in the assessment of drugs, especially as such disturbed breathing patterns may represent part of a continuous spectrum of response with at one extreme excessively long apnoeas and dangerous hypoventilation.

Minute volume (V\textsubscript{L}) represents the temporal summation of a series of individual breaths, but it is often more informative to interpret changes in minute volume in terms of the average breath. Each breath may be subdivided into tidal volume (V\textsubscript{T}) and timing components (inspiratory and expiratory times T\textsubscript{I} and T\textsubscript{E}, total breath time T\textsubscript{tot}) (Milic-Emili and Grunstein, 1976; Remmers, 1976; Milic-Emili and Aubier, 1980). We may derive

\[
\dot{V} = V_T \times f = \frac{V_T}{T_{tot}} = (\frac{V_T}{T_I}) \times (\frac{T_I}{T_{tot}})
\]

where f = respiratory rate. V\textsubscript{T}/T\textsubscript{I} may be considered to represent inspiratory drive and T\textsubscript{I}/T\textsubscript{tot} to represent the proportion of time taken up by inspiration, or the inspiratory duty cycle (fig. 1). This separation of breathing into drive and timing elements enables changes in pulmonary ventilation to be interpreted as alterations in either or both components (see below and figure 7) and may enable sites of actions of drugs to be localized.

Problems and precautions

Resting ventilation is readily altered by a variety of stimuli. Care is needed to eliminate such stimuli in order to reduce variability in measurements and avoid misinterpretation of drug effects. Subjects should be well informed about the nature of the tests and procedures. They should have adequate prac-
Nitrous oxide administered in analgesic concentrations (20% and 40%) to normal volunteers was found to decrease end-tidal $PCO_2$ predominantly through an increase in respiratory rate (Royston, personal communication). In the same study, using respiratory inductive plethysmograph coils around thorax and abdomen, it was shown that nitrous oxide diminished the rib cage contribution to tidal breathing (Royston, Jordan and Jones, 1981). A similar finding was made by Rigg and Rondi (1981) using magnetometers to study the effects of morphine on chest wall movement, suggesting that the rib cage contribution to breathing may be highly susceptible to the effects of central depressant drugs. These authors argued that this finding may have practical implications in that morphine may be a special hazard for patients who are dependent on increased intercostal or accessory muscle activity to maintain adequate ventilation. Patients with hyperinflation as a result of chronic obstructive lung disease or patients with increased abdominal respiratory loading as a consequence of obesity or abdominal surgical procedures may therefore be particularly susceptible to the effects of morphine or other central depressant drugs.

As may be anticipated, most volatile anaesthetic agents decrease ventilation and increase resting arterial or end-tidal $PCO_2$ in proportion to the concentration that is administered (Munson et al., 1966). It is notable that the administration of respiratory depressant drugs to anaesthetized patients is associated with a greater degree of respiratory depression than would be predicted from their effect on $PCO_2$ and ventilation in conscious volunteers (Potter and Payne, 1970). For example, in one study (Hunter, 1967) respiratory arrest occurred in three of 13 patients given diazepam 2.5–10 mg during anaesthesia with nitrous oxide, oxygen and halothane, whereas the effect of diazepam 15 mg on resting end-tidal $PCO_2$ in normal volunteers was to produce only a small increase of 0.2 kPa (Jordan, Lehane and Jones, 1980).

Using magnetometers, Tusiewicz, Bryan and Froese, (1977) showed that halothane anaesthesia considerably diminished the rib cage contribution during quiet breathing, a finding supported by Jones and colleagues (1979) using mercury-in-silastic strain gauges. It was concluded that a major part of the depression of ventilation associated with halothane resulted from suppression of intercostal muscle function. Subsequent lack of recruitment of rib cage activity with increased chemical drive, and
loss of active stabilization of the rib cage by intercostal muscle contraction resulted at times in paradoxical inward movement of the rib cage during inspiration. Such effects suggest that patients who are normally dependent on intercostal muscle activity may be more prone to hypoventilation while breathing spontaneously during halothane anaesthesia (Tusiewicz, Bryan and Froese, 1977). The suppression of rib cage activity by halothane, together with the central depressant effect on the ventilatory response to carbon dioxide (Ngai, Katz and Farhie, 1965; Munson et al., 1966), explain the quite profound effects of halothane anaesthesia on ventilation.

TESTS OF CHEMOSENSITIVITY: RESPONSE TO HYPERCAPNIA

In normal man a highly sensitive control mechanism regulates arterial carbon dioxide tension within narrow limits, despite widely varying carbon dioxide production rates. Increases in carbon dioxide tension in arterial blood stimulate the peripheral arterial chemoreceptors directly and the central chemoreceptors in the brain indirectly through concomitant changes in brain extracellular pH. The respiratory centres situated in the pons and medulla respond to the information from the chemoreceptors and maintain arterial PCO₂ relatively constant by regulating ventilation. Drugs may well operate at one or more sites in this process although the difficulty in distinguishing between the individual components of the response to carbon dioxide has meant that most drug studies have dealt with the response of the system as a whole. Several techniques have been used to assess the ventilatory response to carbon dioxide, and they may be subdivided into either steady-state or nonsteady-state methods.

Steady-state methods

The steady-state method is the classical approach for assessing the effect of inhaled carbon dioxide on ventilation. The subject breathes various fixed concentrations of carbon dioxide (e.g. 3, 5, 6 and 7%) for periods of about 20 min to allow time for arterial blood and brain extracellular carbon dioxide and hydrogen ion concentrations to approach a steady state. Towards the end of this period the alveolar PCO₂ (or preferably arterial PCO₂) is measured together with the response to this stimulus which is usually the ventilatory minute volume. If PCO₂ is plotted against minute volume, an almost linear relationship is found, the slope of which (S) represents the sensitivity of the ventilatory response to carbon dioxide, expressed as the change in ventilation per unit change in PCO₂. The intercept of the line with the zero ventilation axis, obtained by extrapolation, may also be measured.

Hypercapnia increases the ventilatory response to hypercapnia and so in order to examine the response to carbon dioxide alone, hyperoxic conditions should be used (arterial PO₂ greater than 20 kPa). Useful information can be obtained by repeating the steady-state procedure at progressively lower arterial oxygen tensions (e.g. 13.3 kPa, 6.7 kPa) and plotting PCO₂ against minute volume for each oxygen tension (fig. 2). This is the classical way to assess the interaction between carbon dioxide and hypoxia (Lloyd, Jukes and Cunningham, 1958). One of the practical problems of the test, which has been extensively reviewed by Cunningham (1974), is that it is extremely time-consuming. Merely to plot one response line may take an hour and this is clearly a limitation of its usefulness in testing the effects of drugs. A further limitation is that long periods of hypercapnia and possibly hypoxia may alter the absorption, distribution or metabolism, of drugs (Dempsey, 1976). Severinghaus (1976) has proposed a more rapid pseudo steady-state method for determining the ventilatory response to hypoxia and hypercapnia and this may be appropriate for drug studies.

![Fig. 2. The effect of oxygen tension on the ventilatory response to hypercapnia.](https://academic.oup.com/bja/article-abstract/54/7/763/308143)
Nonsteady-state methods

Rebreathing techniques

These techniques, which involve generating a progressively increasing carbon dioxide stimulus, have become routine in many laboratories largely as a result of their convenience and speed. The rebreathing techniques described by Read (1967) is generally used and involves the subject rebreathing from a small bag containing carbon dioxide with an initial concentration at or slightly above the mixed venous carbon dioxide concentration. The bag is usually primed with a volume approximately equal to the subject’s vital capacity plus 1 litre and the mixture is usually hyperoxic (e.g. 7% carbon dioxide, 50% oxygen, balance nitrogen). After 30–60 s of rebreathing, the $PCO_2$ in the bag equilibrates with alveolar gas and arterial and mixed venous blood so that $PCO_2$ at these locations, and presumably at the chemoreceptor sites, changes at the same rate. Carbon dioxide tension increases steadily with time at a rate of approximately 0.4–0.8 kPa min$^{-1}$ and this produces a steadily increasing stimulus to ventilation. Oxygen tension, although decreasing progressively, is maintained greater than 20 kPa throughout the rebreathing period (usually about 4–6 min). To ensure hyperoxia at the start of rebreathing, the subject usually breathes 50% oxygen for several minutes beforehand.

Carbon dioxide tension measured in the rebreathing gas mixture defines the stimulus to breathing since it is in equilibrium with arterial and mixed venous blood and it is therefore unnecessary to take arterial blood samples. As in the steady state test, a virtually linear relationship between minute volume and $PCO_2$ is normally found, although non-linearity is often seen at lower $PCO_2$ (hockey stick appearance) and the line is shifted to the right of the steady-state response. There is no significant difference between the slopes of the ventilatory response as assessed by steady state or rebreathing methods in the absence of metabolic alkalosis or acidosis (Read, 1967), although differences between the two methods have been observed in subjects with chronic acid–base disturbances (Linton et al., 1973).

Practical aspects. The rebreathing method in its simplest form requires a relatively modest outlay in equipment. Rebuck (1976) has described “...in cookbook style, the ingredients of the rebreathing circuit, along with the operating instructions.” Basically, such a system uses a rebreathing bag enclosed in a rigid, airtight container which is connected to a volume measuring device such as a dry gas meter. With this arrangement, often referred to as a “bag-in-bottle”, the subject breathes to-and-fro from the bag causing room air to leave and enter the container through the volume measuring device. Alternatively, the rebreathing bag may be replaced by a spirometer filled to the required volume (Jordan, 1981). End-tidal $PCO_2$ is measured close to the mouth with a rapidly responding carbon dioxide analyser and the sampled gas should preferably be returned to the rebreathing bag. A carbon dioxide response line may be obtained by plotting mean ventilation $v.$ end-tidal $PCO_2$ calculated over successive 30-s intervals during rebreathing. The first point should be calculated during the first 30-s interval following equilibration between $PCO_2$ in the bag and the lungs as indicated by a steady “mixed venous plateau” in end-tidal $PCO_2$. The slope and intercept of the ventilatory response line may then be calculated by least squares linear regression. Automatic methods may be used to produce breath-by-breath plots of “instantaneous” minute volume (tidal volume $\times 60/\text{T}_{\text{rot}}$) against end-tidal $PCO_2$ and this considerably simplifies data analysis (Milledge, Minty and Duncalf, 1974).

Special precautions. Despite the fact that the rebreathing method is technically straightforward, many workers have encountered problems in producing reliable and reproducible results. All of the problems and precautions stated above in assessing ventilation and blood-gases are particularly relevant to rebreathing experiments. Further precautions include the following. The subject should breathe 50% oxygen in nitrogen through the mouthpiece for 5 min before testing and only be connected (via a wide-bore tap) to the rebreathing circuit when end-tidal $PCO_2$ is stable ($\pm 0.2$ kPa). The airflow resistance of the rebreathing circuit should be low (e.g. $<0.25$ kPa litre$^{-1}$ s at 2 litre s$^{-1}$) and if a non-rebreathing valve is used it should be free from sticking. Rebreathing tests should not be repeated more frequently than once every 15 min. Body temperature has been shown to affect the ventilatory response to carbon dioxide (Cunningham and O’Riordan, 1957) and should be recorded and controlled if necessary by use of blankets or cooling fans. There is wide variability in the slope of the ventilatory response to carbon dioxide between individuals and therefore it is advantageous for subjects in drug trials to act as their own controls. Day-to-day variability within individuals is also large, but may be reduced by ensuring measurements are made at the same time of day at a set time (e.g. 2 h).
after a light meal and after 30 min rest in the laboratory. Although variability in measurements within days is smaller than that between days (Sahn et al., 1977) it is advantageous to make duplicate or triplicate measurements and to follow the time-course of a possible drug effect by making measurements serially rather than simply pre- and post-drug. The distribution of slopes of the ventilatory response to carbon dioxide in the population is log-normally skewed (Irsigler, 1976; Mustchin, 1977) and the effects of drugs on slopes appears to be related to initial values, so it is preferable to perform statistical tests on slope data after taking logarithms.

“Mouth occlusion pressure” response to carbon dioxide rebreathing. The ventilatory response to carbon dioxide normally represents the overall sensitivity of the respiratory centre to the carbon dioxide stimulus. However, there are circumstances in which the response of the respiratory centre may be unchanged but the ventilatory response to carbon dioxide may be reduced, for example when there are increased mechanical loads to breathing as in patients with obstructive lung disease. In order to obtain more direct measures of respiratory centre output, techniques have been developed which involve recording integrated phrenic nerve activity (Eldridge, 1975) and measurement of the diaphragmatic electromyogram (Lopata et al., 1978). These methods are technically difficult and not easily applied in patients. However, good correlation has been shown between the integrated diaphragmatic electromyogram and the airway pressure developed shortly after the start of inspiration against a transiently occluded airway (Eldridge, 1975; Lopata, Evanich and Lourencço, 1977). This technically simple and non-invasive measurement, usually referred to as “mouth occlusion pressure”, is not affected by resistance or compliance of the respiratory system since there is no airflow and no change in lung volume during the occlusion. Mouth occlusion pressure increases linearly with carbon dioxide tension, as does the electromyographic activity of the diaphragm (Altose et al., 1976; Zubillaga et al., 1976), and its rate of increase with carbon dioxide may be used as a more direct measure of the response of the chemoreceptors and respiratory centre. It may therefore be a useful method in drug assessment when the mechanical properties of the lung or chest wall, or both, are likely to alter or in studying patients with obstructive lung disease.

Special precautions. It is necessary to measure the airway pressure soon after the commencement of inspiratory effort to avoid conscious responses and volume-related reflexes. Several groups measure the pressure at 100 ms ($P_{0.1}$) after the start of inspiratory effort (Whitelaw, Derenne and Milic-Emili, 1975; Altose et al., 1976; Jordan, 1981), although a survey of various times of sampling suggested that 175–200 ms provides more reproducible data (Yoshida et al., 1981). Brief occlusions are difficult to produce with manually operated valves and so an automatic method has been developed in which a solenoid valve occludes the airway briefly (for 120 ms) at the start of inspiration on selected breaths during a carbon dioxide rebreathing procedure (Jordan, 1981). The subatmospheric pressure generated in the airway may be displayed (fig. 3) and the pressure at 100 ms sampled and plotted automatically against end-tidal carbon dioxide tension (fig. 4). The ventilatory response to carbon dioxide may be assessed simultaneously with the $P_{0.1}$ response since the brief occlusions do not perturb ventilation.

In studies on the effects of drugs on the mouth occlusion pressure response to carbon dioxide, it is necessary to take into account the effects of any changes in functional residual capacity as these may influence the force of inspiratory muscle contraction for a given neuronal drive (Shaffer et al., 1977). The plot of occlusion pressure with time is not always linear (Whitelaw, Derenne and Milic-Emili, 1975; Kryger, Yacoub and Anthonisen, 1975) and could alter its shape with drugs and this should be considered before extrapolating from changes in measurements made early in inspiration.

![Fig. 3. Superimposed tracings of mouth occlusion pressure plotted against time as carbon dioxide tension increases during a rebreathing procedure. From Jordan (1981) by permission of the Editor of Medical and Biological Engineering and Computing.](https://academic.oup.com/bja/article-abstract/54/7/763/308143)
Tests of transient responses to carbon dioxide

These non-steady state methods have been developed to quantitate non-invasively the sensitivity and speed of response of the peripheral and central chemoreceptors. A single vital capacity breath of 15% carbon dioxide produces a brief increase in ventilation which is readily detectable (Gabel, Kronenberg and Severinghaus, 1973). If the inhaled carbon dioxide is reduced, then the ventilatory responses are comparable to the spontaneous changes that occur during normal breathing. To increase the resolution of the response, the tests may be carried out while the subject breathes a hypoxic gas mixture or alternatively the response to a large number of tests may be averaged. Ward and Cunningham (1977) used alternate-breath inhalation of carbon dioxide and averaged the response over many breaths. Sohrab and Yamashiro (1980) applied step changes in carbon dioxide concentration between 0 and 6.8% on a breath-by-breath basis in a random sequence determined by a pseudorandom binary sequence generator. Cross-correlation analysis of this input with the ventilatory response yielded estimates of impulse responses and an indirect estimation of peripheral chemoreceptor sensitivity to carbon dioxide and lung to chemoreceptor time lag. Although tests of the transient response to carbon dioxide have the advantage of rapidity and are unaffected by secondary adaptive responses, the technical complexity involved in producing good resolution and reproducibility of response has so far led to relatively little exploitation of such tests in testing the effects of drugs.

Examples of the effects of drugs on the response to carbon dioxide

Ventilatory response to carbon dioxide. The rebreathing technique has been fairly extensively applied in assessing the effects of drugs on the ventilatory response to carbon dioxide. Some reported results are summarized in table I.

It has been shown that increasing concentrations of most volatile anaesthetic agents produce increasing depression of the slope of the ventilatory response to carbon dioxide together with a shift in intercept to the right (Larson et al., 1969). Knill and Gelb (1978) showed that 1.1 and 2 MAC concentrations of halothane produced a dose-related depression of the slope of the ventilatory response to carbon dioxide, although 0.1 MAC had no effect. In similar experiments, enflurane was shown to pro-

<table>
<thead>
<tr>
<th>Drug (source)</th>
<th>Reduction in slope of ventilatory response to carbon dioxide (%)</th>
</tr>
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<tbody>
<tr>
<td>Morphine 7.5-10 mg i.m.</td>
<td>30-40</td>
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<tr>
<td>(Jennett, Barker and Forrest, 1968; Weil et al., 1975; Jordan et al., 1979; Rigg and Rondi, 1981)</td>
<td></td>
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<tr>
<td>Pethidine 75 mg i.m.</td>
<td>50</td>
</tr>
<tr>
<td>(Engineer and Jennett, 1972)</td>
<td></td>
</tr>
<tr>
<td>Pentazocine 45-60 mg i.m.</td>
<td>33-36</td>
</tr>
<tr>
<td>(Engineer and Jennett, 1972; Jordan et al., 1979)</td>
<td></td>
</tr>
<tr>
<td>Meptazinol 100 mg i.m.</td>
<td>7</td>
</tr>
<tr>
<td>(Jordan et al., 1979)</td>
<td></td>
</tr>
<tr>
<td>Diazepam 14 mg i.m.</td>
<td>50</td>
</tr>
<tr>
<td>(Jordan, Lehane and Jones, 1980)</td>
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duce dose-related depression of the carbon dioxide response slope with a significant depression at 0.1 MAC (Knill, Manninen and Clement, 1979). Tusiewicz, Bryan and Froese (1977) studied the relative contributions of rib cage and diaphragm to ventilation during carbon dioxide rebreathing and showed that halothane virtually abolished the increase in rib cage contribution which is normally seen during rebreathing (Pengelly, Tarshis and Rebuck, 1979).

Mouth occlusion pressure response to carbon dioxide.
Morphine 10 mg was shown to depress the slope of the $P_{O_2}$ response to carbon dioxide by approximately 35%, with good correlation between the slopes of the ventilatory and $P_{O_2}$ responses to carbon dioxide, which was the expected result in normal subjects with no pulmonary mechanical impairment (Jordan, 1981) (fig. 4). Diazepam was shown to depress the $P_{O_2}$ response to carbon dioxide to 50% of control, a result similar to the reduction in ventilatory response (Jordan, 1981). Derenne and colleagues (1976) found that methoxyflurane anaesthesia reduced the ventilatory response to carbon dioxide but not the mouth occlusion pressure response, possibly implying that the main action of the anaesthetic was to impair the mechanical properties of the respiratory system rather than to depress the respiratory centres.

TESTS OF CHEMOSENSITIVITY

RESPONSE TO HYPOXIA

Although acute changes in ventilation are predominantly under control of the feedback process involving regulation of carbon dioxide and hydrogen ion concentration, chronic adjustments of ventilation are often governed mainly by oxygen requirements. In patients with chronic carbon dioxide retention resulting from severe lung disease, the extracellular fluid pH in the brain and the blood pH may be near normal in spite of the increased arterial $PCO_2$. Most of the stimulus to breathing from the increased $PCO_2$ is therefore diminished and arterial hypoxaemia is the main drive to ventilation. Many drugs considerably depress the ventilatory response to hypercapnia and if they also depress the response to hypoxia then profound respiratory depression is likely.

Hypoxia stimulates ventilation primarily through its action on carotid body chemoreceptors and has no action on central chemoreceptors, other than a depressant effect in severe hypoxia. The ventilatory response to abrupt changes in oxygen tension is very rapid (approx. 10–20 s) and this provides a brisk protective reflex during events such as the upper airway obstruction that may occur during normal sleep (Bowes et al., 1981). A drug that depresses the response to hypoxia may therefore have deleterious effects on this protective reflex. In the overall assessment of the respiratory effects of pharmacological agents, testing the respiratory response to hypoxia would therefore seem highly relevant.

Steady-state methods

The ventilatory response to hypoxia is measured by the subject breathing various fixed concentrations of oxygen for periods of at least 5–10 min before ventilation is measured. End-tidal $P_{O_2}$, or preferably arterial $P_{O_2}$, is used to quantitate the stimulus to breathing. It is usual to maintain end-tidal or arterial $PCO_2$ at a constant value during the increased ventilation produced by hypoxia by adjusting the inspired concentration of carbon dioxide. This method (Cormack, Cunningham and Gee, 1957) enables ventilation to be plotted as a function of $P_{O_2}$ for each value of $PCO_2$. The resulting function can be reasonably fitted by a hyperbola, the shape of which reflects the sensitivity to hypoxia. Methods of processing such data are described in the next section. The results may also be plotted as shown in figure 2 as the ventilatory response to carbon dioxide at different but constant values of $P_{O_2}$ (Cunningham et al., 1957; Lloyd, Jukes and Cunningham, 1958). The response to hypoxia may then be evaluated by comparing the slopes of the ventilatory response to carbon dioxide under conditions of differing $P_{O_2}$. A further approach is to measure the difference in ventilation produced by arterial oxygen tensions of 6 kPa (40 mm Hg) and 25 kPa at resting arterial $PCO_2$, referred to as $AV_{40}$ (Sørensen and Severinghaus, 1968). This technique has the disadvantage that only one point during hypoxia is used, and this point is usually in a region where ventilation is likely to vary greatly with small changes in $P_{O_2}$ or $PCO_2$ (Weil and Zwillich, 1976).

Equilibration of the arterial oxygen chemoreceptors with inspired oxygen is fairly rapid and the period of breathing required to reach a steady state may be reduced by first equilibrating with the inspired carbon dioxide. However, the steady-state tests involve rather prolonged exposure to hypoxia and may be hazardous to some patients. Methods have therefore been developed for assessing the ventilatory response to hypoxia which require somewhat shorter exposure to hypoxic gas mixtures.
Nonsteady-state methods

The ventilatory response to isocapnic hypoxia may be derived as a continuous curve relating alveolar oxygen tension to minute volume by two basic methods.

Progressive technique

A gradual reduction of inspired oxygen concentration is achieved by the controlled addition of nitrogen to the inspired gas mixture and the addition of carbon dioxide to maintain PCO$_2$ constant (Weil et al., 1970). The time taken for alveolar Po$_2$ to reach 6-7 kPa is approximately 10-20 min and is controlled by the investigator.

Rebreathing technique

The subject rebreathes from a 6-litre bag containing an initial mixture of 30% oxygen, 7% carbon dioxide (approx. mixed venous concentration) and nitrogen (Rebuck and Campbell, 1974). Oxygen concentration in the circuit gradually decreases as a result of metabolic consumption while PCO$_2$ is kept constant by manually adjusting the amount of rebreathed gas which passes through a carbon dioxide absorber. The time taken for alveolar Po$_2$ to decrease to 6-7 kPa is approximately 4-6 min.

End-tidal oxygen may be measured using a rapidly responding fuel cell oxygen analyser (Weil, Sodal and Speck, 1967) or a mass spectrometer and the end-tidal carbon dioxide tension may be measured with a rapidly responding infra-red analyser or mass spectrometer. Ventilation may be measured using one of the methods described above. The rebreathing technique may utilize a "bag-in-bottle" to enable indirect measurement of ventilatory volumes and so avoid problems of the effects of changes in gas composition on the volume measuring device.

These methods yield data that are comparable to the steady-state technique, and have the advantage of being quicker to carry out. A hyperbolic relationship between ventilation and Po$_2$ at constant PCO$_2$ usually assumed and the equation for the hyperbola that best fits the data is calculated. This relationship can be described by the equation

\[ \dot{V} = \dot{V}_0 + A(\text{PAO}_2 - C), \]

where \( \dot{V} \) is minute ventilation, \( \dot{V}_0 \) is the value of ventilation if PAO$_2$ (alveolar oxygen tension) were to approach infinity; \( A \) is the parameter which determines the shape of the curve and \( C \) is the value of PAO$_2$ at which ventilation would approach infinity (fig. 5). The equation is applicable to data obtained by steady-state, progressive or rebreathing methods for assessing the isocapnic hypoxic ventilatory response. The effect of a change in chemoreceptor sensitivity to hypoxia is to alter the shape of the hyperbola and to change the value of \( A \) (fig. 5).

The value of \( C \) is usually taken as 4.27 kPa (32 mm Hg) and this enables \( \dot{V} \) to be related to \( 1/(\text{PAO}_2 - 4.27) \), resulting in a virtually linear relationship, with a slope \( A \) and intercept \( \dot{V}_0 \) which may be determined by linear least-squares regression (Weil et al., 1970). It may, however, be preferable to use a curve-fitting method that does not assume a value for \( C \) (Hey and Hey, 1960). When oxygen concentration is plotted against ventilation, a virtually linear relationship is seen (Weil et al., 1970) and the same applies to oxygen saturation as measured by ear oximetry (Rebuck and Campbell, 1974; Rebuck and Woodley, 1975) (fig. 6). This may therefore provide a suitable means of determining the hypoxic response when rapid oxygen analysis is unavailable or when end-tidal Po$_2$ poorly reflects arterial Po$_2$.

Special precautions

Many of the precautions stated above apply to testing the response to hypoxia. If the hypoxic response is to be measured at a PCO$_2$ greater than the...
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normal resting arterial value, a period of equilibration should be allowed (possibly 6–10 min) before inducing hypoxia. (Read, Nickolls and Hensley, 1977). Because of the marked effect of a change in PCO₂ on the hypoxic response, it is essential to control PCO₂ within close limits during the test. As for the hypercapnic ventilatory response, the hypoxic ventilatory response is more variable between-days than within-days (Sahn et al., 1977) and therefore it is desirable to assess the effects of drugs over a short time course if possible, preferably using baseline data obtained on that day. It may well be that hypoxic ventilatory responses are log-normally distributed, as are hypercapnic ventilatory responses, but this has not yet been proven.

Careful monitoring of the subject’s cardiovascular status is required to prevent possible deleterious effects of hypoxia.

Tests of transient response to hypoxia

Single or multiple breaths of nitrogen are administered and the resulting change in ventilation over the next 15–30 s is recorded. The test is rapid to perform, does not involve prolonged periods of hypoxia and therefore avoids the central depression sometimes produced. However, the response is small and lacks resolution and reproducibility unless the stimulus is combined with hypercapnia (15% carbon dioxide in nitrogen) (Kronenberg et al., 1972) or unless multiple response averaging techniques are used.

Examples of the effects of drugs on the response to hypoxia

The few studies of the effects of drugs on the response to hypoxia in man have been mainly confined to testing the ventilatory response to progressive or rebreathing hypoxia. Weil and others (1975) showed that, in normal volunteers, morphine 7.5 mg produced a significant decrease in A (to 40% of control), greater than the depression in the slope of the ventilatory response to carbon dioxide. A greater depression in the hypoxic response than the hypercapnic response following morphine 15 mg was also reported by Santiago and colleagues (1979). Hirshman and his colleagues (1975), also using progressive isocapnic hypoxia, showed that pentobarbitone has a depressant effect on A in some individuals. Knill and Gelb (1978) showed that halothane virtually abolished the hypoxic response at 1.1 and 2 MAC concentrations, and caused a reduction to 28% of control at 0.1 MAC, suggesting that halothane has a more important effect on the hypoxic response than on the hypercapnic response. Similar observations were made for enflurane (Knill, Manninen and Clement, 1979).

Mouth occlusion pressure may be used to quantify the change in ventilatory drive to breathing during hypoxia in a way similar to the method described for use during hypercapnia. Kryger and others (1976) found that pethidine depressed both the ventilatory and Pₒᵢ responses to hypoxia to a greater extent than the depression of the hypercapnic responses.

MEASUREMENT OF RESPONSE TO ADDED MECHANICAL LOADS

Patients with obstructive airways disease, such as bronchial asthma, frequently exhibit greater than normal respiratory depression after narcotics (Crofton and Douglas, 1981) and it seems reasonable to establish whether loaded breathing per se has deleterious effects on ventilation which may be exacerbated by certain drugs (Pengelly, Rebuck and Campbell, 1973). Although loads may be added to breathing by inhalation of bronchoconstrictor agents, the ethics, logistics and interpretational problems considerably limit this method and it is more usual to apply some form of external mechanical load, of which there are three main types:
Resistive loads: where pressure across the load depends on flow rate through it. These resistances may be a simple narrow tube, but it is more usual to use a resistance that is roughly constant with flow over the normal range, such as a tube containing a series of fine wire mesh discs or uniformly packed cotton wool.

Elastic loads: where pressure across the load depends on the volume displacement. These are usually constructed from closed tanks or drums from which the subject breathes — the smaller the drum, the smaller the compliance.

Threshold loads: where pressure across the load is constant once a flow is established. These are most easily constructed from a pipe partially immersed in water at a depth set by the threshold pressure required.

The response to the load may be measured in terms of (a) its effect on volume, flow, pressure or timing, (b) changes in nervous activity at various sites or changes in pattern of movement of the chest wall, or both and (c) changes in blood-gases. The normal response depends on the type of load but generally it results in the maintenance of a nearly normal minute volume, even in the face of large loads. The normal response to an inspiratory resistive load is a prolongation of the inspiratory phase and a low inspiratory flow rate. The responses are conveniently divided into early and steady-state changes with chemical factors being important only in the latter. The early response to a mechanical load operates through the stretch receptors, muscle spindles and the intrinsic mechanical properties of the inspiratory pump (Cumming and Semple, 1980), whereas after one or two breaths the chemical drive to ventilation becomes increasingly important. A major factor governing the response to a load is the volitional or conscious response, especially as this may be modified by learning. Drugs may act at one or more points in the regulatory process or may interfere with the interaction of the various components. For example, an analgesic drug may interfere with chemosensitivity and thus alter the steady-state response to a load, but it may also interfere with the conscious interpretation of the load through its analgesic and sedative properties. Although the response to an extrinsic load in healthy subjects may be different to that in patients with intrinsic loads increased through pulmonary disease (Anthonisen, 1976), it may well be that drugs act in a similar way in both situations. Hence studying the change in responses to a load in normal subjects may give indications of the expected effects in patients with obstructive airways disease.

Examples of reported effects of drugs on loaded breathing

The effects of drugs on loaded breathing are not always predictable from their effects on chemosensitivity. Normal subjects given the analgesic drug meptazinol showed no significant alteration in the ventilatory response to carbon dioxide, but end-tidal carbon dioxide tension during inspiratory resistive loading was increased to a similar value as during loading following an equivalent dose of morphine (Jordan et al., 1979). In contrast, diazepam was shown to depress the ventilatory response to carbon dioxide but did not adversely alter the response to an inspiratory resistive load (Jordan, Lehane and Jones, 1980).

Light general anaesthesia with methoxyflurane has been shown to reduce considerably the response to inspiratory resistive loading (Whitelaw et al., 1976) as indicated by relative lack of increases in drive and inspiratory time with loading. In a study on the effects of sub-anaesthetic concentrations of nitrous oxide on the response to inspiratory resistive loading in volunteers, a considerable reduction in the immediate (first breath) response to the load was found with nitrous oxide (Royston, Jordan and Jones, 1981). The normal prolongation of inspiratory time and increased tidal volume were not apparent with nitrous oxide (fig. 7) although inspiratory drive, as assessed by VT/TI, was unchanged. It is likely that the immediate response was largely consciously mediated and therefore that nitrous oxide reduced the awareness of the load. Indeed only two of the eight subjects in this study stated awareness of the load during 40% nitrous oxide. This relative lack of awareness to loading seems a recurring feature of analgesic drugs and may be important clinically as it may indicate possible failure of adequate response to partial or total upper airway obstruction. The effect was independent of altered chemosensitivity, since nitrous oxide does not depress the ventilatory response to carbon dioxide (Eckenhoff and Helrich, 1958; Yacoub et al., 1976).

A further important aspect of the load-compensating response is the stabilization of the chest wall against deformation or distortion in the face of loading, so that the respiratory muscles may function efficiently (Shannon and Zechman, 1972). For example, inspiratory loading can result in in-
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ward movement of the rib cage on inspiration as a result of large subatmospheric intrathoracic pressures produced predominantly by diaphragmatic contraction. Such paradoxical movement of the rib cage would require the diaphragm to contract more to produce a given tidal volume and may also alter the distribution of ventilation in the lung and lead to impaired ventilation-perfusion matching. Using the respiratory inductive plethysmograph in a study of the effects of nitrous oxide on loaded breathing, a marked increase in asynchronous breathing was found with 40% nitrous oxide (Royston, Jordan and Jones, 1982). Compared with air breathing measurements, there was a diminished rib cage contribution to tidal volume and an increased phase shift between rib cage and abdominal movement during loaded breathing on 40% nitrous oxide. It has also been shown that halothane anaesthesia depresses both phasic and tonic postural reflex activity of the rib cage, resulting in paradoxical movement during resistive loading (Jones et al., 1979).

The above reports are all concerned with the effect of a single stress applied to the ventilatory control system. It is possible to apply simultaneously multiple stresses to the system, for example loading and exercise (Demedts and Anthonisen, 1973) or loading and increased chemical drive (Kryger et al., 1976; Lopata et al., 1977). Santiago and others (1980) studied the respiratory response to hypercapnia with and without added inspiratory resistance and showed that acute administration of methadone abolished the augmentation of inspiratory drive (assessed by mouth occlusion pressure) normally seen with loaded breathing (fig. 8). In contrast, chronic methadone administration did not result in reduced response to the load and the authors therefore concluded that narcotic drugs may abolish the respiratory compensation although tolerance develops with chronic use. Meperidine has been shown to reduce the response to external resistance during hypercapnia and hypoxia, and this was interpreted as the drug producing “non-recognition” of the load or inhibiting the motor response to a load that was recognized (Kryger et al., 1976).

**ASSESSMENT OF RESPIRATORY EFFECTS OF DRUGS IN A CLINICAL ENVIRONMENT**

With the possible exception of the anaesthetic agents, respiratory effects of drugs have been studied in detail only in normal subjects in the laboratory, with relatively few detailed reports of their effects on respiration in patients in the clinical environment. It is difficult to extrapolate with confidence from the effects of a drug on the regulation of breathing in normal subjects to the effect that it may have in patients in differing clinical situations. There are several practical problems in applying conventional

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**Fig. 7.** The average respiratory cycle as in figure 1, showing the first loaded breath while subjects breathed air, 20% and 40% nitrous oxide. The mean data for eight subjects are shown and illustrate the lack of prolongation of inspiratory time with loading while breathing nitrous oxide and an unchanged inspiratory drive as indicated by an almost fixed slope of the inspiratory portion ($VT/Ti$).

**Fig. 8.** Effects of methadone on the ventilatory and mouth occlusion responses to hypercapnia with and without inspiratory resistive loading. Methadone depressed the unloaded response to hypercapnia and almost completely abolished the normal increase in the mouth occlusion pressure response to hypercapnia with loading. Redrawn from Santiago and others (1980) by permission of the authors and the Editor of the American Review of Respiratory Disease.
tests for assessing control of breathing in patients. In applying these tests it is usually necessary to familiarize the patient with the respiratory manoeuvres and apparatus beforehand and this is not always possible. The patients may be drowsy, confused or in pain and this will limit co-operation as well as influencing the results in an unpredictable fashion. A further important aspect is that it may be potentially hazardous to apply stress tests involving hypercapnia, hypoxia or mechanical loads in patients. During sleep the respiratory effects of drugs may further diminish normal reflex function (Forrest and Bellville, 1964; Sullivan et al., 1978), and so it is important to examine the effects of drugs on the control of breathing during sleep. Most conventional tests are applicable only to awake patients.

In the opinion of the author, it is more relevant to evaluate the action of clinically administered drugs on resting breathing in the undisturbed patient rather than on artificial challenges which would then require interpretation and extrapolation to situations that occur naturally. Measurements of normal resting breathing in the clinical environment play a vital role in the overall assessment of a pharmacological agent or particular method of administration and although many of the problems of applying conventional challenge tests in patients are avoided, new problems emerge which are challenging to the investigators.

**Requirements of clinical assessment**

The effects of respiratory depressant drugs on the pattern of breathing are often quite marked, resulting for example in periodic breathing or in occasional apnoeic episodes. To detect these transient events it is necessary to make continuous measurements over periods of many hours. The monitoring methods should therefore be comfortable and unobtrusive to the patient, should require virtually no patient co-operation and should preferably be non-invasive.

**Measurement of ventilation.** Mouthpieces or tight-fitting face-masks enable direct measurement of ventilation, but they are poorly tolerated by patients for long periods of measurement, cause conscious awareness of breathing, increase deadspace and restrict movement. Mouthpieces have been shown to alter significantly the pattern of breathing (Gilbert et al., 1972). Methods which measure ventilation without direct connection to the airway are better suited to long-term continuous assessment of respiration. Techniques which measure changes in external dimensions of the torso may be calibrated against a direct method of volume measurement to yield quantitative data. Methods which enable the measurement of the separate contributions to breathing of the rib cage and abdomen—diaphragm are preferable as they also allow recognition of paradoxical or asynchronous breathing and separate identification of obstructive and central apnoeas. Most methods to date involve measurement of cross-sectional dimensions (e.g. anteroposterior and lateral dimensions using magnetometers) or circumference (e.g. using mercury-in-silastic strain gauge). As discussed earlier, there are limitations in the accuracy of such techniques in situations where the pattern of breathing or posture of the patient may change, or when distortion of the shape of the chest wall may occur (as in increased mechanical loading, such as airway obstruction). It may therefore be preferable to use the more recent approach of respiratory inductive plethysmography which is commercially available as Respitrace. The device is comfortable to wear and is ideally suited to long term recordings. It has been demonstrated to provide good accuracy of volume measurement over a wide range of body positions (Watson, 1980), and is frequently used in monitoring respiration during sleep both in adults in sleep disorder centres and in infants in special care units (Duffy et al., 1981).

In interpreting measurements of ventilation, it is often necessary to consider the state of consciousness of the patient. Unlike measurements of normal volunteers where periods of sleep should be avoided, measurements of resting breathing in patients in the normal clinical environment may encompass periods of differing sleep stage as well as wakefulness. It has been well documented that normal sleep significantly alters breathing, with different sleep states or stages having different effects (Bulow, 1963; Gothe et al., 1981). Care must be taken to ensure that changes in breathing induced by normal sleep should not be misinterpreted as drug effects. Further, it is possible that respiratory depressant drugs act synergistically with sleep to depress respiration seriously (Forrest and Bellville, 1964), and with depressed protective reflexes this could constitute a considerable hazard. In order to assess the interaction between sleep, drugs and respiration, recordings of the electroencephalogram (e.e.g.), electrooculogram (e.o.g.) and electromyogram (e.m.g.) may be analysed using conventional sleep staging techniques and criteria (Rechtsaffen and Kales, 1968; Agnew and Webb, 1972).
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Measurement of blood-gas tensions. Direct methods of blood-gas measurement are invasive and unsuitable for continuous long-term measurements and it is preferable to use indirect methods. End-tidal $\text{PCO}_2$ may be sampled using a mass spectrometer or infrared carbon dioxide analyser, but if a mouthpiece or face-mask is to be avoided, the gas sampling line will need to be placed at the nares or in the nasopharynx with possible problems of air entrainment, moisture blockages and discomfort to the patient. Arterial oxygen saturation may be estimated using ear oximetry and this is a convenient and reasonably accurate method which is well suited to long term continuous measurements.

Examples of respiratory effects of drugs in a clinical environment

Gas exchange is often impaired in patients after anaesthesia and major surgery (Marshall and Wyche, 1972), so that the effects of respiratory depressant drugs may be more profound during the initial postoperative period. Consequently the assessment of respiration is necessary in the development and evaluation of improved techniques for providing analgesia after operation. There is currently much activity in this field, conventional opiate and the newly developed analgesics being administered as continuous i.v. infusions, as variable rate infusions in patient demand systems, and as intrathecal and extradural injections. Few studies have included a sufficiently comprehensive assessment of respiratory depression, most relying simply on intermittent measurements of respiratory rate and blood-gas tensions.

In a study of patients who had undergone cholecystectomy, respiratory inductive plethysmography was used to record respiration continuously for 24 h after surgery (Catling et al., 1980) and revealed that continuous i.v. infusion of papaveretum (mean dose 145 mg in 48 h) was associated with a greater frequency of apnoeic episodes and periods of low respiratory rates than conventional intermittent injections (81 mg in 48 h). Apnoeic periods lasting up to 40 s and rates as low as 6 b.p.m. were recorded.

In a subsequent study to investigate possible interactions between opiate analgesia, sleep and residual effects of anaesthesia, one group of patients received a continuous infusion of morphine following an i.v. pain relieving dose, and another group received intercostal nerve block with bupivacaine (Catley et al., 1982). E.g., e.g., oxygen saturation using ear oximetry, and respiration using respiratory inductive plethysmography enabled disturbances in breathing to be quantitated and related to sleep state during the 16-h study period. Oxygen saturation frequently decreased to less than 80% in several patients receiving morphine, with most of these events being associated with periods of partial or total upper airway obstruction as indicated by paradoxical motion of rib cage or abdomen respiratory signals and by audible snoring in many cases (fig. 9). Many episodes of central apnoea were also observed although oxygen saturation never decreased to less than 89% during these events (fig. 10). The potentially most serious events were therefore associated with upper airway obstruction, presumably resulting from loss of tone of the muscles of the upper airway allowing the tongue to fall back or the pharyngeal walls to collapse (Guillemainault et al., 1978). These events always occurred during stages 1 or 2 of sleep and were usually terminated by an arousal or awakening (fig. 9). None of the patients were in stage 4 or REM sleep during the study and very few were in stage 3.

During periods of partial upper airway obstruction, tidal volume and minute volume were frequently seen to increase progressively during the episode whilst paradoxical chest wall movements increased and oxygen saturation decreased dramatically (fig. 11). This illustrates the inadequacy of simple measurements of rate or even tidal volume without provision for recognizing paradoxical breathing (i.e. separate rib cage and abdominal signals). The end-expiratory volume often decreased during such periods (fig. 11) and this may have contributed to the decrease in oxygen saturation. Continuous measurement of end-expiratory volume may therefore be informative in relating respiration to changes in oxygenation, particularly in patients with diminished lung volumes such as patients after abdominal surgery, or those with closing capacity near to or greater than functional residual capacity.

A further observation in this trial and in a similar study (Ford, et al., 1981) was that diaphragm function is often considerably depressed following upper abdominal surgery, even during adequate analgesia, so that patients become reliant on intercostal muscle activity. The preferential suppression by morphine of the rib cage contribution to breathing observed in normal volunteers by Rigg and Rondi (1981) and during sleep by Tusiewicz and colleagues (1977) could therefore be hazardous to such patients. In
FIG. 9. Partial airway obstruction developing into obstructive apnoea in a patient receiving a morphine infusion for pain relief following total hip replacement. Note the paradoxical respiratory movements and the marked decrease in oxygen saturation terminated by an arousal (as indicated by the e.e.g. and e.o.g.) and the re-occurrence of normal breathing. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.

FIG. 10. Episode of central apnoea lasting 30 s in a patient who received an intercostal nerve block for pain relief after cholecystectomy. Note the relatively small decrease in oxygen saturation during the period of apnoea. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.
FIG 11. Repeated episodes of paradoxical respiration (caused by partial upper airway obstruction) in a patient receiving morphine infusion for pain relief following total hip replacement. The marked decreases in oxygen saturation during periods of paradoxical respiration were terminated by hyperventilation and then followed by prolonged respiratory pauses (12 s and 17 s). Note the decreasing oxygen saturation despite the increasing ventilation during the periods of paradoxical respiration. The insets show two breaths at the beginning and end of a period of paradoxical respiration and indicate the development of paradoxical movement of the rib cage late in inspiration and early in expiration. The oxygen saturation trace is delayed by 10–15 s because of lung–ear circulation time and instrument response time.

addition, the suppression of chemosensitivity by morphine may account for the general impairment of blood-gas tensions found in patients receiving larger doses of papaveretum (Catling et al., 1980). It may also explain why patients receiving morphine analgesia appear to arouse from sleep at lower oxygen saturations during periods of apnoea and partially obstructed breathing than do patients receiving non-opiate analgesia (Catley et al., 1982).

CONCLUSION

By utilizing techniques such as those used in the study of patients with disturbed breathing during sleep (e.g. sleep apnoea syndrome) the effects of drugs on both transient and steady-state respiration may be established in the clinical environment and such changes related to sleep state. Furthermore, it is evident that the results of tests in normal volunteers in the laboratory may be usefully applied to a particular clinical situation and that the two very different fields of assessment of respiratory effects of drugs can be complementary.
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