Oxygen therapy

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OXYGEN enrichment of the inspired air is widely used in clinical practice in the treatment of conditions such as myocardial infarction, heart failure, pneumonia and cor pulmonale with the intention of preventing or correcting tissue hypoxia. Usually oxygen therapy carries no dangers; occasionally, when hypoxaemia has been the main source of ventilatory drive, giving oxygen may cause severe underbreathing, leading to serious harm.

It is therefore important that the indications for oxygen administration are clearly understood, and also that the potential dangers which may follow its injudicious use are recognized.

Mechanism and indications of tissue hypoxia

Theoretical aspects

Oxygen is present in the atmosphere in a concentration which varies little from 20.9%; the tension of oxygen varies according to the barometric pressure (P_B) and at sea level in dry air has a tension of 0.209 mmHg. Within the air passages where the air contains water vapour at a tension of 47 mmHg the oxygen tension is $0.209 \times (P_B - 47)$ mmHg. For example, at a P_B of 760 mmHg, the tension of oxygen in the inspired air in the trachea is 150 mmHg. This is the maximum pressure of oxygen available to the body under normal circumstances. As oxygen is transferred in turn from the atmosphere to the alveolar gas, in the circulation from lungs to tissue capillaries, through the extracellular fluid, to the surface of the tissue cell, and through the cell membrane and the cell cytoplasm to the sites where it will be utilized in the oxidative processes, there is a progressive reduction in oxygen tension. Tissue PO_2 is generally considered to be about 35 mmHg but the PO_2 at the intracellular site will be lower. Indeed, some oxygen utilization is believed to persist at a PO_2 less than 1 mmHg.

In disease, the pressure drop in certain of these processes of O_2 transfer may become greater than normal, in which case intracellular PO_2 may become too low to permit these processes to proceed normally.

Under normal conditions of increased tissue requirements for oxygen, such as occur in the muscle cell during exercise, oxygen supply to the intracellular site is maintained by two mechanisms. First, the

increased rate of utilization of oxygen causes a lowering of the local PO_2 , which facilitates transport to the intracellular site; and secondly, the opening up of collapsed capillaries shortens the mean diffusion pathway from blood to cell; together these two factors cause a steeper gradient for oxygen diffusion enabling it to take place at a greater rate. Regional circulatory adjustments together with an increased cardiac output provide the increased oxygen flow to the capillaries to ensure that the proximal end of this diffusion gradient is maintained fairly constant even under conditions of very heavy exercise (Mitchell, Sproule & Chapman, 1958).

In disease which may require intensive care, e.g. myocardial infarction or acute respiratory failure, even the resting cell may become hypoxic. This is because the failure of the pulmonary and/or circulatory systems to transport oxygen at an adequate rate to the tissue capillaries may cause such a reduction in the capillary PO_2 that the diffusion gradient between the blood and the intracellular site is insufficient to supply oxygen to meet the needs of even a resting cell.

Because of the multiplicity of processes involved in oxygen transport from the atmosphere to the intracellular site of utilization it is obvious that a single measurement along the route will necessarily reveal whether the supply to the tissues is adequate or not. Thus, cardiac output and arterial saturation alone do not give information about O_2 flow. Even O_2 flow measurements may be inadequate because they have to be related to O_2 consumption; and even with this information, knowledge of diffusion pathways is required to estimate whether tissue or cellular PO_2 will be adequate or not.

It follows, therefore, that to decide whether tissue hypoxia is present or not, we must look to the tissues rather than to the transport mechanism for firm objective evidence of tissue hypoxia (Howell, 1966). There is general agreement that the only readily measurable tissue metabolite which increases as a result of oxygen lack, and which appears in the general circulation, is lactic acid; and also that an elevation of blood lactate necessarily indicates tissue hypoxia only when the ratio of lactate to pyruvate (L/P ratio) is increased (Huckabee, 1958c). It is, of course, necessary that the hypoxic tissues must

receive some perfusion for the tissue levels to be reflected in the blood.

Relationship of reduced arterial oxygen content to tissue hypoxia

Although tissue hypoxia may occur in the presence of normal arterial oxygen levels, low arterial PO_2 does not always imply tissue hypoxia. The observations of Huckabee (1958) on dogs and on normal man made hypoxic by reduced O_2 concentrations in the inspired air, and the observations of Penman (1962) on acute respiratory failure in patients with chronic bronchitis and emphysema suggest that tissue hypoxia will occur in the presence of an adequate circulation when the arterial PO_2 falls below 40 mmHg and the oxygen saturation below 65%. For this reason, the suggestion of Hutchison *et al.* that the PO_2 should not be allowed to fall below 50 mmHg would seem to provide a considerable margin of reasonable safety. However, the recent observations of Eldridge (1966) would appear to set the safe limit at an even lower level in this condition. He has reported that in a group of patients with acute respiratory failure there was no alteration in L/P ratios in any of them despite PO_2 as low as 30.2 mmHg, $\text{Sao}_2 < 65\%$, as long as there was a good circulation.

Relationship of reduced blood flow to tissue hypoxia

When cardiac output falls in animals there is some evidence that O_2 consumption is reduced (Guyton, 1966), but it is not reported whether L/P ratios change to indicate the development of tissue hypoxia.

In patients with and without cardiogenic shock following myocardial infarction the cardiac index may fall to approximately 2.0 l/min before L/P ratios alter and, by inference, significant tissue hypoxia occurs, even though in addition arterial unsaturation is commonly present (MacKenzie *et al.*, 1964).

In treating these patients it is imperative that the reduced blood flow be made to carry as much oxygen as possible, by the efficient administration of 100% O_2 . When tissue hypoxia is present the local acidosis will help to maintain the capillary PO_2 due to its effect in shifting the O_2 dissociation curve to the right.

Practical considerations

Rather than limit the use of oxygen therapy to conditions of unequivocal need, clinicians prefer to work with a margin of safety by maintaining O_2 levels above the critical level for tissue hypoxia. This is obviously sensible as long as harm is not done in the process.

Therefore, in most conditions of severe arterial

unsaturation due to pulmonary disease, e.g. pneumonia, acute pulmonary oedema, acute diffuse interstitial pulmonary inflammation (Hamman-Rich), pulmonary atelectasis, the highest O_2 levels which seem appropriate to the situation and which can conveniently be obtained should be sought. It would help in future judgments about O_2 therapy if, from time to time, some objective measurements of need were made.

The decision about need for O_2 therapy is much more important if such therapy can cause harm. This is the situation with many cases of acute exacerbations of chronic diffuse obstructive disease of the airways—'chronic bronchitis and emphysema'. Because it is virtually the only situation where O_2 therapy (excluding hyperbaric oxygen) can cause harm, it will be considered in more detail later.

In conditions of reduced blood flow encountered clinically, e.g. myocardial infarction, measurement of cardiac output is rarely feasible or even desirable and other indices of the danger of tissue hypoxia must be used if rational O_2 therapy is to be given. These include clinical evidence of inadequate circulation, and laboratory evidence of raised L/P or the development of metabolic acidosis (Neaverson, 1966). However, since there is no danger of hypoventilation following O_2 administration in this situation, and the aim is to increase O_2 content as much as possible, it is reasonable practice on the mere suspicion of hypoxia to 'soak' the patient in oxygen by any convenient means. An arterial blood sample taken at the outset would enable laboratory confirmation of need to be obtained at leisure.

The dangers of oxygen therapy

The continuous administration of 100% O_2 may result in changes in the lungs of animals. It is possible that this may occur in man but this theoretical danger should never inhibit the use of 100% O_2 if tissue hypoxia would otherwise occur.

The main danger of O_2 therapy in clinical practice occurs in the case of patients with acute ventilatory failure associated with severe diffuse airway narrowing, most commonly due to so-called chronic bronchitis and emphysema, but also with status asthmaticus.

The rational use of oxygen in these types of patient requires an understanding of the pathophysiology of the disease processes.

Oxygen therapy in chronic bronchitis and emphysema *Patho-physiology of the disease causing oxygen lack*

The typical patient with 'chronic bronchitis and emphysema' has developed the following changes:

(i) Bronchial mucous gland and goblet-cell hyperplasia resulting in the production of increased volumes of sputum causing expectoration.

(ii) Hyper-reactivity of the bronchi to inhaled

irritants or to the local irritation of bronchial infection.

(iii) Diffuse narrowing of the airways of varying severity.

(iv) Variable degrees of overinflation of the lungs which may be localized or generalized, and which may involve only the central part of some lobules (centrilobular emphysema) or the whole lobule (panacinar emphysema).

The effect of these changes on individual patients will vary depending upon their severity and their distribution, but in general can be considered under these headings:

(a) *Mechanical*, causing (i) increased effort to ventilate the lungs and therefore dyspnoea, and (ii) impairment of the process of coughing.

(b) *Ventilatory*. (i) If the airway narrowing becomes very severe, it may not be possible to ventilate the lungs with the muscular power available and for other mechanical reasons. This appears to apply to asthmatics and the true 'pink puffers'. (ii) In others, there is a coincident reduction of true CO_2 responsiveness so that underbreathing occurs without the diffuse airway narrowing necessarily being very severe.

The combination of airway narrowing and emphysema, particularly the centrilobular type, often leads to a reduction in the ventilation of regions of the lung whose blood flow is maintained relatively normal. As a result blood flowing through these regions becomes incompletely oxygenated and arterial unsaturation results. It is not uncommon for 30% or more of the cardiac output to be 'shunted' through underventilated portions of the lungs.

This summarizes the typical situation in patients when they are relatively well and in a steady state. If these patients are given 100% oxygen to breathe the increased oxygen tension in the inspired air is sufficient to penetrate even into the poorly ventilated regions in sufficient quantity to completely saturate the blood which perfuses them. Almost as much is achieved by administering only 30% oxygen because this increases the inspired oxygen tension by over 60 mmHg. *It is important to note that even 100% does not cause the patient to underbreathe to any serious degree*—the PCO_2 usually rising less than 10 mmHg. Trouble arises from the administration of oxygen only when the patient develops an acute worsening of the mechanical state of his lungs. This may be due to an acute bronchial infection or to exposure to irritants, with the following consequences: (1) increased secretions from the bronchi causing obstruction, (2) further narrowing due to bronchial hyperactivity, (3) further disturbance of V/Q causing arterial unsaturation (hypoxaemia), and (4) despite the increased ventilatory drive caused by the hypoxaemia the increased mechanical difficulty causes underbreathing with elevation of the PCO_2 .

In the majority of patients, a balance is reached where the hypoxaemic drive is powerful enough to overcome the increased mechanical load to inspiration. Sometimes, however, even this drive is insufficient and progressive underbreathing and hypoxaemia occur leading to death of the patient. If oxygen is given to the patient in this state sufficient to relieve the hypoxaemia, it will lead to underbreathing. If this is marked and prolonged the patient may lose consciousness. Here oxygen administration can convert the relatively alert, co-operative patient into one who cannot co-operate in his own bronchial toilet and he may asphyxiate in his own secretions. McNicol & Campbell (1965) have shown that few patients who have not been given oxygen have PCO_2 greater than 80 mmHg. This situation is not confined to the patient with chronic bronchitis and emphysema who has impaired responsiveness to CO_2 ; it may also occur in the asthmatic with very severe airways obstruction, and I have seen one such patient deeply unconscious with a PCO_2 of 270 mmHg! However, this is no condemnation of oxygen administration to the severe asthmatic. It merely reflects the severity of the narrowing of the airways, and without oxygen the patient would have died.

Practical aspects of oxygen administration in the chronic bronchitic with airways obstruction

The foregoing considerations enable a rational approach to O_2 therapy in this situation which may be summarized as follows:

(i) *For the man who has complete facilities*, i.e. full blood-gas and acid-base measurements on arterial or arterialized capillary blood.

(a) *The need for oxygen*. This is not always obvious and a need is more often considered to be present when it is not than overlooked when it is needed.

Clinical. Severe cyanosis, signs of poor cardiac output in the form of low-volume pulse, ashen colour and sweating, and/or grossly impaired consciousness are an indication for immediate administration of oxygen. When the pulse is full and bounding it is less likely that immediate O_2 is indicated.

Laboratory. Arterial $\text{PCO}_2 > 75\text{--}80$ mmHg, $\text{Po}_2 < 40$ mmHg and O_2 saturation $< 65\%$ suggest that even if tissue hypoxia is not already present there is little margin of safety, and an attempt should be made to bring the oxygen levels at least up to these values.

The presence of an increasing metabolic acidosis or increasing L/P ratio indicates an urgent need for improved arterial saturation.

(b) *Serial observations*. The aim of serial observations is to judge whether adequate oxygenation of the arterial blood is being achieved and also whether this is leading to progressive underbreathing. Thus if

an arterial $\text{Po}_2 > 40$ mmHg can be maintained without the PCO_2 rising progressively, this aspect of management is probably satisfactory. Failure to achieve this oxygen level indicates that the concentration of inspired oxygen requires to be increased further. A rapid *initial* rise in PCO_2 of up to 10 mmHg is to be expected; a *progressive* rise is cause for concern. Should such a rise occur, a decision must be taken whether the oxygen inspired can be reduced to increase hypoxaemia and therefore ventilation, or whether this would result in dangerous hypoxia. In the latter case, if it is certain that bronchial toilet has been carried out with maximum efficiency by intensive skilled physiotherapy, if necessary following the administration of analeptics and aminophylline intravenously, then tracheal intubation with suction and assisted ventilation may be necessary. The extent to which PCO_2 should be permitted to rise will vary according to the initial level; the lower the initial level the less likely it is to rise abruptly. There are no hard-and-fast rules for the permitted upper limit; in my view, because the only real harm done by an elevated PCO_2 is to reduce the patient's ability to co-operate in his own bronchial toilet by coughing, this is a more valuable end-point than any absolute figure for the PCO_2 .

The frequency with which arterial blood measurements are made will depend on the individual circumstances. Whenever there is doubt about the clinical situation, a further sample should be analysed.

(ii) *For the man who has facilities limited to a Campbell rebreathing set* (Campbell, 1960a)

(a) *The need for oxygen.* More reliance will have to be placed on clinical judgment based on the signs described above.

A rebreathing $\text{PCO}_2 > 75$ –80 mmHg would support a decision for O_2 therapy. Note that neither cyanosis nor marked respiratory distress are in themselves indications of tissue hypoxia and the need for O_2 administration.

(b) *Serial measurements.* The effectiveness of O_2 therapy will have to be judged on clinical grounds, but the likelihood of progressive underbreathing may be anticipated by serial rebreathing PCO_2 measurements. No attempt should be made to abolish the central cyanosis until it is certain that progressive underbreathing will not result. Any hospital which is unable to make such measurements should not undertake the treatment of these patients.

The administration of oxygen

There are two different requirements according to the clinical situation. Where reduced tissue oxygenation is due to reduced blood flow, then the highest concentration of oxygen in the inspired gas must be sought. The details of obtaining this with face mask

or oxygen tent are well described elsewhere (e.g. Pask, 1958).

Similarly in most situations of reduced oxygen content due to pulmonary disease, oxygen therapy administered by face mask or O_2 tent is desirable, except when the treatment may cause underbreathing. In this circumstance, control of the degree of O_2 enrichment of the inspired air is needed, and methods are available by which this may be achieved with different degrees of success. These have been described elsewhere (Campbell, 1960b; Campbell & Gebbie, 1966; Flenley, Hutchison & Donald, 1963) and will only be reviewed briefly here.

Venturi methods

(a) *Face mask.* Campbell (1960b) described a face mask with which the oxygen content of the gas delivered could be varied from 24% to 35% with high gas flows. Subsequently, the manufacturers have made a mask with a fixed Venturi delivering approximately 28% oxygen. This mask is suitable for the majority of patients as it is relatively infrequently that a satisfactory arterial Po_2 cannot be obtained.

(b) *Head tent.* More recently Campbell & Gebbie (1966) have described the use of a variable Venturi device with a small tent fitting loosely over the head and shoulders. With this a wide range of total flows and O_2 concentrations can be obtained. This overcomes the disadvantage of the fixed O_2 concentration delivered by the Ventimask and also has the advantage that it is usually better tolerated than the face mask, especially by confused patients.

Nasal catheters have been used for decades. They are usually well tolerated by patients, but have the disadvantage that high O_2 concentrations may be given unwittingly, and cannot be detected if arterial blood monitoring is not available.

However, when such measurements are employed, it is a very satisfactory method.

The Edinburgh mask is a close fitting, low dead-space, face mask in which oxygen is added at controlled rates (Flenley *et al.*, 1963). It is claimed that by varying the oxygen flow, the concentration inspired by the patient can be varied from 22% to 35% with an accuracy acceptable for clinical purposes.

Conclusions

(1) The greatest uncertainty in this field is to know when oxygen is needed by the patient.

(2) In practice, if there is doubt about need, oxygen should be given in high concentration because it will do no harm to the majority of patients.

(3) In patients with diffuse airways obstruction, only sufficient oxygen to prevent hypoxia should be given and serial measurements of arterial PCO_2 should be made to observe whether relief of hypoxaemia is causing progressive underbreathing.

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