Gas goes in and out
Blood goes round and round
Part 1

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CONTENTS

GAS GOES IN AND OUT: BLOOD GOES ROUND AND ROUND COMMON PHYSIOLOGICAL MISCONCEPTIONS IN ANAESTHESIA AND CRITICAL CARE

Part 1: Gas goes in and out.

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Anaesthesiologists are the medical specialists most concerned with gas exchange. The beep of the pulse oximeter is ubiquitous in operating theatres and ICUs and the tone as the saturation reduces is one of the most powerful stimuli for action by anaesthesiologists.

Meticulous recording of blood pressure, pulse rate, saturation and end tidal CO_2 is one of the first skills acquired by trainee anaesthetists. Unfortunately, some of the interventions employed to reverse hypoxia, hyper/hypocarbia, hyper/hypotension and/or brady/tachycardia and may worsen the situation, as they are based on imperfect understanding of the underlying pathophysiology.

HYPOXIA

Pioneering work from anaesthesiologists working on Mount Everest has revealed the remarkable tolerance of humans to hypoxia [1]. Arterial blood gases take at The Balcony (8400m above sea level) are remarkable for at least 2 reasons:

1. The gases could be taken at all given the oxygenation of those doing the arterial punctures.
2. The mean PaO_2 and saturation levels were 24.6 and 54% respectively.

While the participants in this trial were fit and highly motivated, and thus very different from the average patient in the operating theatre and ICU, they do demonstrate that humans may be able to tolerate much lower levels of oxygenation than previously thought.

CLASSIFICATION

Hypoxia is traditionally categorised as:

Reduced
- •Stagnant: Cardiac output
- •Anaemic: Haemoglobin concentration
- •Cytotoxic: Mitochondrial function
- •Hypoxic Arterial oxygen tension

A common misconception that arises from this classification is that the causes are equally important. In reality, stagnant, anaemic and cytotoxic hypoxia have clear diagnostic signs that differentiate them both from one another and from the most relevant cause of hypoxia in anaesthesia and critical care, hypoxic hypoxia.

HYPOXIC HYPOXIA

⬇ FiO$_2$

Hypoxic gas mixtures are unusual in the practice of anaesthesia and critical care outside the special situations of high altitude (hypobaric) or deep diving (hyperbaric) environments.

Under anaesthesia and in ICU, the FiO$_2$ is routinely maintained at above 0.3 so a hypoxic gas mixture as a cause of hypoxic hypoxia is rare. South Africa is unusual in that the majority of the population lives at moderate altitude and are thus chronically exposed to a lower PiO$_2$ than populations living at sea level. Supplemental oxygen will also generate a lower PiO$_2$ for the same FiO$_2$ at altitude [2].

AIRWAY OBSTRUCTION

One of the most important skills acquired and practiced daily by anaesthesiologists is maintenance of a clear airway. Oxygenation requires communication between the lungs and the atmosphere via a patent airway from the mouth, through the pharynx, trachea, conducting airways to the alveoli.

There are a wide variety of options to fulfil this goal from a simple facemask to supraglottic devices, endotracheal tubes and invasive options including tracheostomy.

Tidal ventilation is not required to maintain oxygenation as demonstrated by the absence of desaturation following intubation and connection to the breathing circuit without initiation of mechanical ventilation, a process known as apneic oxygenation.

V/Q MISMATCH

This term is used blithely by trainees in anaesthesia and critical care but understanding of the term may be sadly lacking [3]. The classic diagram representing V/Q mismatch is shown in Fig 1.

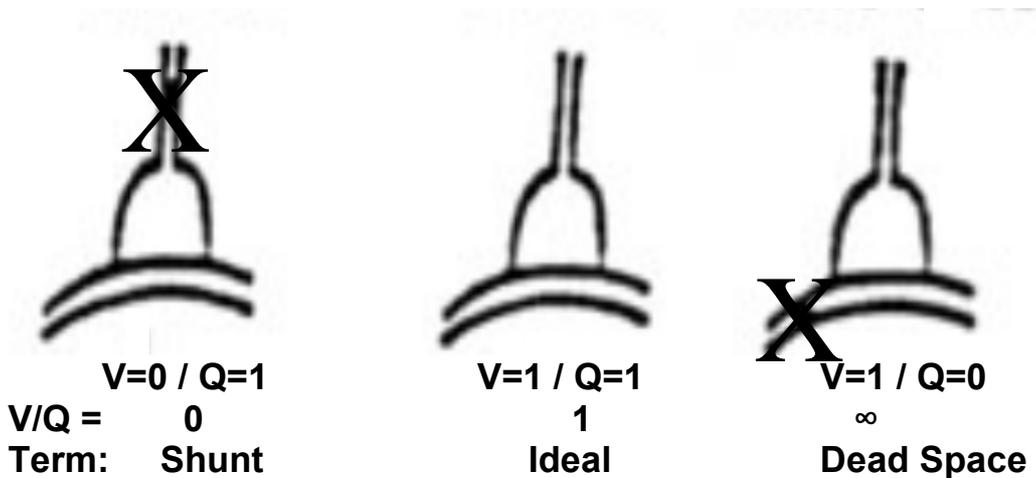| V=0 / Q=1	V=1 / Q=1	V=1 / Q=0
V/Q = 0	1	∞
Term: Shunt	Ideal	Dead Space

Fig 1: Relationship between Ventilation (V) and Perfusion (Q)

Traditionally shunt is represented by a bronchial obstruction. While such obstructions do occur and are treated by physiotherapy and bronchoscopy if required they are far from the commonest cause of shunt. In fact the vast majority of shunts in the operating theatre and ICU have two far more common causes:

1. **Alveolar Collapse [4]**
   Atelectasis results from initiation of mechanical ventilation with positive pressure. The process occurs in healthy patients who lie supine under general anaesthesia and is even more marked in ICU patients with acute lung injury (ALI). The reason is a change in gas distribution with positive as opposed to negative pressure ventilation [5]. The volume of the human lung lies predominantly posteriorly, in relation to the bulk of muscle in the diaphragm (Fig 2).
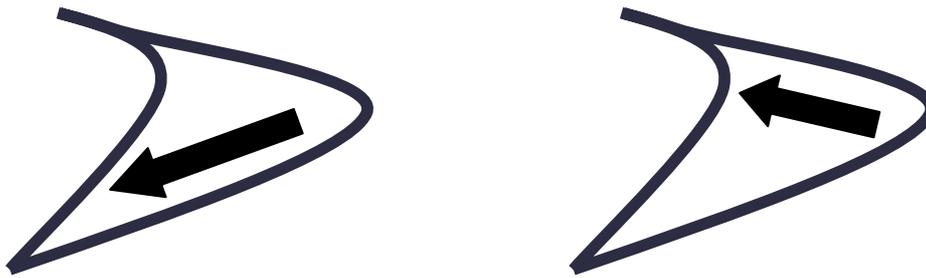
Negative Pressure   **Positive Pressure**

Figure 2: Distribution of lung volume in supine lungs and gas with positive vs. negative pressure.

Lung expansion with negative pressure generated by the diaphragm is thus maximal in the posterior lung, which is dependent in the supine patient (Figure 2).

Conversely, with positive pressure, gas follows the path of least resistance. In the supine patient, the posterior, dependent lung has narrower airways than the anterior, non-dependent lung. Gas under positive pressure is thus preferentially distributed to the anterior, non-dependent lung, resulting in progressive collapse (Fig 2).

This collapse can be clearly seen on CT scanning [6], which is impractical outside research units in the first world. An alternative method of assessing collapse is multiple inert gas elimination technique that does not require CT scanning [7].

2. Alveolar Flooding

Thickening of the alveolar membrane, thus increasing diffusion distance, or speeding of circulation to reduce the time spent by red blood cells traversing alveolar capillaries are largely theoretical reasons for incomplete oxyhaemoglobin saturation and thus arterial hypoxia [8].

These are, however, minor causes of hypoxia in the operating theatre or ICU. In reality, the most common reason for haemoglobin to remain desaturated after passing through the lungs is that the alveolar capillaries are filled with fluid so that the red cells are never brought into proximity with respiratory gas [9]. Alveolar flooding is thus the most common cause of shunt in the clinical practice of anaesthesia and critical care.

Alveolar fluids [10]

a. **Blood:** most commonly as a result of pulmonary contusion but can be due to bronchial / bronchiolar haemorrhage.

b. **Exudate:** disruption of the alveolar epithelium and/or epithelium results from infection resulting in the consolidation characteristic of pneumonia. A similar pattern may be seen with aspiration or inhalation of hot or toxic gas.

c. **Transudate:** arises due to pathological alterations in the Starling equation across the alveolar capillary membrane (Fig 3).

$$Q = k(P_c - P_i) - \sigma(\pi_c - \pi_i)$$

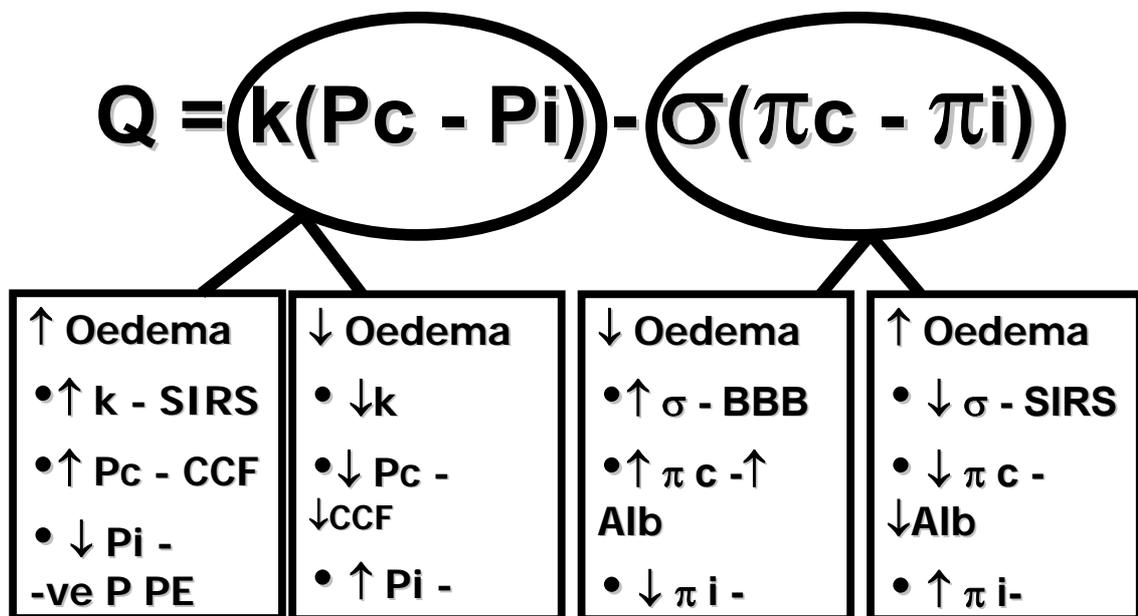| ↑ Oedema	↓ Oedema	↓ Oedema	↑ Oedema
• ↑ k - SIRS	• ↓ k	• ↑ σ - BBB	• ↓ σ - SIRS
• ↑ Pc - CCF	• ↓ Pc - ↓CCF	• ↑ π c -↑ Alb	• ↓ π c - ↓Alb
• ↓ Pi - -ve P PE	• ↑ Pi -	• ↓ π i -	• ↑ π i-

Figure 3. The Starling equation showing the influences on fluid flux across the alveolar epithelium.

1. **Increased capillary hydrostatic pressure (Pc):** is seen most frequently with congestive cardiac failure (CCF) but may also be seen with absolute hypervolaemia, most commonly due to renal dysfunction. Fluid overload, in the absence of cardiac or renal dysfunction, is exceedingly rare [11].

2. **Reduced filtration coefficient (k):** is seen with disruption of the alveolar capillary membrane as seen in the systemic inflammatory response syndrome (SIRS) or sepsis resulting in Acute Lung Injury (ALI) worsening to the Adult Respiratory Distress Syndrome (ARDS) [12]. The alveolar capillaries are equally affected by SIRS / sepsis but fluid is exuded under the influence of gravity, less in the non-dependent and more in the dependent areas of the lung – the "sponge lung" concept of ALI/ARDS [13].

d. **Patterns of Alveolar shadowing on CXR** [14]

1. **Contusion:** seen in relation to an overlying injury, usually rib fractures. Reabsorption of blood and reconstitution of alveolar function is slow, over a period of days.
2. **Consolidation:** in a lobar distribution is characteristic of pneumonia.
3. **Diffuse:** diffuse shadowing has a very wide differential from bronchopneumonia, including SIRS / sepsis and cardiac failure. Clinical context is vital with fever and constitutional symptoms and signs characteristic of bilateral pneumonia and ALI / ARDS. The characteristic feature of ALI / ARDS compared with CCF is sparing of the costophrenic angles in ALI/ARDS.

e. **Cause and duration of flooding**

1. **Cause** [15]
   i. **Primary (Pulmonary):** aspiration, inhalation as well as both lobar and bronchopneumonia primarily affect the lungs with an inflammatory alveolar exudate.
   ii. **Secondary (Extra-pulmonary):** a process affecting the endothelium throughout the body, such as SIRS or sepsis, results in a transudate in the lungs through the damaged alveolar capillary endothelium.

2. Duration [16]

    i. **Early (within 48-72 hours):** the earlier the flooding the more likely it is to be reversible by managing the underlying cause as seen with rapid response to therapy of CCF and pneumonia (with early appropriate antibiotics).

    ii. **Late (after 3-5 days):** flooding is most likely to persist in the presence of inflammation, which also induces a fibrotic response. The longer the inflammatory response persists, the greater the likelihood of flooding being replaced by fibrosis, which limits reversibility.

MANAGEMENT OF HYPOXIA: ATELECTASIS VS. ALVEOLAR FLOODING

Atelectasis can be re-expanded by the application of positive pressure. Conversely fluid cannot be displaced from the alveoli by positive pressure. Atelectasis may be differentiated from flooding by CT scan but this is impractical outside research centres.

Atelectasis is most likely in patients with normal lungs receiving a general anaesthetic.

PREVENTION AND TREATMENT OF ATELECTASIS UNDER ANAESTHESIA [17]

Atelectasis is prevented by immediate application of positive end expiratory pressure (PEEP) on initiation of mechanical ventilation. If PEEP is not applied hypoxia will result within 20-30 minutes. The process is accelerated by increased intra-abdominal pressure from factors such as reverse-Trendelenberg position, obesity and pneumoperitoneum. Raising FiO_2 will paradoxically worsen hypoxia as oxygen will be absorbed from small alveoli precipitating collapse, a process known as absorption atelectasis.

The treatment of hypoxia under general anaesthesia is a controlled inflation:

Vital capacity breath: 20cmH$_2$O for 5 seconds

A vital capacity breath is superior to the late application of PEEP, which will re-expand collapsed alveoli, but these will rapidly collapse when the PEEP is removed at the end of the case.

By contrast, a vital capacity breath maintains alveolar patency by redistributing surfactant that has been clumped during the collapse. A vital capacity breath at the end of the case will limit postoperative atelectasis [18].

Hypoxia in the recovery room is most commonly treated by supplemental oxygen but is better measured by the application of positive pressure by means of mask continuous positive airway pressure (CPAP) that con now be easily applied using a disposable (Boussignac) CPAP system that only requires wall oxygen (Fig 4) [19].

Figure 4. Boussignac disposable CPAP system distributed in South Africa by Viking Medical.

IDENTIFICATION AND MANAGEMENT OF ATELECTASIS IN ICU

In the ICU the differentiation between atelectasis and alveolar flooding is more difficult but flooding is much more likely than with normal lungs under general anaesthesia.

In clinical practice the differentiation can be made by performing a sustained inflation of greater magnitude than the vital capacity breath, known as a recruitment manoevre. The response to the recruitment manoevre will demonstrate whether hypoxia is predominantly due to atelectasis or flooding. A recruitment manoevre involves applying a positive pressure of 40-60 cmH$_2$O over a time period of 20-60sec.

A typical recruitment manoevre is the 40/40 manoevre where a pressure of 40 cmH_2O is applied for 40sec [20].

Contraindications: **Head Injury / Stroke** with raised ICP where fatal increases in ICP have been reported.
Hypovolaemia - acutely reduced preload from raised intra-thoracic pressure may cause cardiac arrest.

Performing a recruitment manoevre:
1. Set FiO_2 to 0.8
2. Set rate to 0
3. Turn off pressure support
4. Set PEEP to 40 cmH_2O
5. Maintain for 40 sec
   a. Monitor BP (arterial line), heart rate and saturation (oximeter)
   b. **STOP EARLY** for hypotension / bradycardia / desaturation
6. Reset PEEP to pre-recruitment level
7. Reset respiratory rate and TV / Pi to pre-recruitment levels

Recruitment manoevres should ideally be performed after every ventilator disconnection but at least 4-6hrly for 24 hours in newly ventilated patients.

Recruitment manoeuvres should be repeated as long as there is a positive response and in the absence of adverse effects.

Arterial blood gas analysis should be performed within an hour of the recruitment manoevre.

A successful manoeuvre will result in [21]:

1. **Improved compliance**
   a. ⇧TV with PCV
   b. ⇩Airway Pressure with VCV
2. **Improved alveolar ventilation**
   a. ⇧PaO_2
   b. ⇩$PaC\,O_2$

An unsuccessful and possibly dangerous manoevre will result in [22]:

> **1. Evidence of overdistension**
>   a. Unchanged or worsened compliance
>   i. Unchanged or ⇩ TV with PCV
>   ii. Unchanged or ⇧ Airway Pressure with VCV
>   b. ⇧ or unchanged PaO_2 – oxygenation may improve with overdistension forcing blood from areas of shunt into perfused alveoli: ⇧West zones 1&2 and ⇩ zone 3
>   c. ⇧ $PaCO_2$ indicating ⇧Physiological dead space / ⇧West zone 1

LUNG PROTECTIVE VENTILATION [23]

After successful recruitment the patient should be ventilated according to the lung protective strategy based on the ARDSnet study showing the benefit of limiting tidal volumes to 6ml/kg. The initial ventilator settings and adjustments are shown in Fig 5.

Setting	Initial	Adjust	Max
• Tidal Volume (ml/kg)	6	1-2	10
• Inspiratory Pressure (cmH$_2$O)	18-22	2-4	35
• Respiratory rate	12-16	1-2	20
• FiO$_2$	0.6-0.8	0.05-0.1	1
• PEEP (cmH$_2$O)	7-12	1-2	20
• Inspiratory time (sec)	1.4-1.6	0.1	2.5 (I:E – 1:1)

Figure 5. Initial ventilator settings with adjustments and maximal settings when ventilating patients with ALI / ARDS in the ICU

Increasing tidal ventilation by volume, pressure, PEEP and/or inspiratory time should be accompanied by careful assessment for over-distension particularly in patients with underlying chronic obstructive pulmonary disease (COPD) and patients with late primary rather than early secondary ALI / ARDS.

REFRACTORY HYPOXIA [24]

The vast majority of hypoxic patients in the ICU will respond to the interventions above. Additional interventions are beyond the scope of this review but include:

1. Alternative modes of ventilation

   a. High frequency oscillation (HFOV)
   b. Airway pressure release ventilation (APRV)

2. Immunomodulation to reduce lung inflammation
   a. Feeding with Ω-3 (fish derived) rather than Ω-6 (plant derived) fatty acids
   b. Administration of steroids: methyprednisolone 1mg/kg in two divided dose daily for 2 weeks followed by 0.5 mg/kg for 2 weeks. Enteral prednisone can be substituted after establishment of enteral nutrition.

3. Prone ventilation
4. Agents most effective in the neonatal transitional circulation
   a. Nitric oxide
   b. Surfactant
   c. Extra-corporeal Membrane Oxygenation (ECMO)

5. Extra-corporeal CO_2 removal (Novalung®)

6. Partial liquid ventilation using perfluorocarbon emulsion

WEANING

Respiratory function should improve with resolution of the underlying disease. Respiratory support should be reduced as function improves and sedation should be minimised. A simple method to achieve this goal is a "sedation vacation" where sedative infusions are stopped every day, most commonly at 0600 [25]. As the level of sedation lightens, patients may be allowed to breathe spontaneously with pressure support at the level of their prior inspiratory pressure [26].

Respiratory rate should be low, tidal volume adequate and patients should not be allowed to tire.

These parameters may be conveniently combined as the **Rapid Shallow Breathing Index (RSBI)** [27]:

RSBI = $\dfrac{\text{Resp Rate}}{\text{Tidal Vol (litres)}}$ e.g. $\dfrac{20}{0.4l \ (400ml)}$ = 50

RSBI	Response
<60	⇓ support
60-80	Maintain current parameters
>80	⇧ support / Recommence controlled ventilation

In reduction of ventilator support, every attempt should be made to maintain recruitment while limiting over-distension. Inspiratory pressure should be reduced after a reduction in shunt is demonstrated by a reduction in FiO_2 requirement. PEEP should only be reduced late, rather than early in the weaning process [28].

Similarly T-Piece trials are redundant in patients who have suffered ALI / ARDS. A traditional T-Piece trial may fail due to the absence of PEEP, which is provided by the upper airway on extubation. In the absence of PEEP recovering lungs may rapidly become atelectatic on a T-piece with hypoxia due to recurrent shunt.
Patients can be extubated directly off the ventilator with PSV of 4-8 cmH_2O and PEEP of 3-5 cmH_2O provided the RSBI is below 60-80. These settings provide just enough support to overcome the resistance of the ventilator and its circuits.

CARBON DIOXIDE MANAGEMENT

Unlike oxygen, that can move down a concentration gradient from the atmosphere to the alveolus in an apnoeic patient, CO_2 requires bulk movement of gas i.e. tidal ventilation, for excretion. In the absence of adequate tidal ventilation, CO_2 will accumulate and cause a respiratory acidosis. Vessels are sensitive to CO_2 across the full range of physiological $PaCO_2$.

Hypocarbia results in vasoconstriction with vasodilation as CO_2 accumulates. The arterial CO_2, which can be inferred from the end-tidal CO_2 measured by capnometry, can be seen as a surrogate marker of alveolar ventilation. Hypocarbia indicates excessive alveolar ventilation while hypercarbia may result from absolute alveolar hypoventilation (TV <5ml/kg / resp rate <8) or relative alveolar hypoventilation (excessive airway pressures with an increased alveolar dead space (Fig 1).

The capnograph is the single most useful monitor of cardiorespiratory function in the operating theatre. Respiratory dysfunction is detected far sooner by capnography than by pulse oximetry [29]. In the resuscitation scenario, capnography will reliably detect endotracheal intubation if the circulation is delivering CO_2 to the lungs and can be used as a surrogate marker for cardiac output during CPR or after restoration of a perfusing rhythm [30].

AVOIDING HYPERVENTILATION

Patients with normal lungs under anaesthesia or after resuscitation are very easy to hyperventilate. The self-inflating bag-valve-mask resuscitation bag has a capacity of 1-1.5l, 3-4 times larger than the desired tidal volume of 6ml/kg (0.45-0.55l). Hyperventilation of patients under anaesthesia, coupled with the residual effects of volatile and/or intravenous anaesthetics and opioids for postoperative pain relief can result in apnoea of a prolonged duration.

This is particularly true for patients with metabolic alkalosis due to gastric outlet obstruction where a compensatory respiratory acidosis is generated by hypoventilation. Anaesthetic hyperventilation will have adverse effects on turnover time between cases and surgical satisfaction but should cause no significant harm to the patient [31].

After resuscitation, however, hyperventilation will substantially worsen outcome by causing cerebral vasoconstriction and extending areas of ischaemic damage. In the post-resuscitation phase, the capnograph should be carefully monitored and correlated with arterial blood gas analysis to ensure normocarbia [32].

MANAGING HYPERCARBIA

Respiratory acidosis in itself is not particularly dangerous. In situations of apneic oxygenation, $PaCO_2$s up to 250mmHg with pHs as low as 6.72 were described in a study on healthy volunteers that is unlikely to be repeated [33]. The cause of hypercarbia should be carefully considered.

The commonest cause under anaesthesia is depletion of the soda lime absorbent in the CO_2 absorber of a circle system [34].

With a functioning absorber, CO_2 can be reduced by increasing alveolar ventilation. This is most frequently attempted by increasing respiratory rate. However, increasing respiratory rate may not always reliably reduce arterial CO_2 for a number of reasons[35]:

a. **Dynamic hyperinflation**: Volume control ventilation with unchanged flow will prolong inspiration to deliver the set breath. Expiratory time will thus be reduced and full exhalation may not occur. Limitation of exhalation is diagnosed by a failure of expiratory flow / pressure to return to baseline at the end of exhalation. This is the start of dynamic hyperinflation that will increase physiological dead space and thus reduce rather than increase alveolar ventilation

b. **Dead space ventilation**:
    i. **Volume control** ventilation with a constant I:E ratio will result in a set tidal volume having to be delivered in a shorter time as respiratory rate increases. This will result in predominant ventilation of dead space rather than alveoli that require more prolonged inflation to participate effectively in gas exchange.
    ii. **Pressure control** ventilation with a constant I:E ratio will result in reduction in tidal volume so, despite an increase in the number of breaths delivered, most of the breaths ventilate dead space rather than alveoli.

In the ICU alveoli may be excluded from gas exchange by collapse or alveolar fluid. While the major manifestation of this process is hypoxia due to shunt, these non-functional alveoli cannot participate in gas exchange so alveolar ventilation will be reduced [36].

This concept of the "baby lung" with limited alveoli available for gas exchange led to the adoption of the approach of permissive hypercapnia [37] where ventilation was adjusted to minimise lung damage while allowing CO_2 to rise.

The utility of this approach was verified by the ARDSnet trial comparing ICU ventilation with tidal volumes of 6 vs. 12 ml/kg that showed a mortality benefit for lower tidal volumes [38]. The trial protocol included guidelines for increasing respiratory rates (max 35) to maintain normocarbia and administration of intravenous bicarbonate to maintain pH 7.3-7.45.

Most units apply the principles of the ARDSnet but allow renal or dialytic compensation for the pH changes rather than increasing respiratory rates or administering bicarbonate.

A gradual increase in CO_2 due to intentional alveolar hypoventilation for lung protection should be distinguished from a step increase in CO_2 in response to a recruitment manoeuvre and/or increased PEEP indicative of hyperinflation and an increased physiological dead space.

Extra-corporeal methods are now available to remove CO_2, which allows tidal volumes as low as 4ml/kg to be used.

The methods include:

    a. Arteriovenous CO_2 removal (Novalung®)
    b. CO_2 removal in the continuous renal replacement circuit (DeCap®)

These interventions add considerable expense and their clinical utility is questionable given the lack of harm associated with permissive hypercapnia.

CLINICAL APPROACH TO HYPERCARBIA IN ADULTS

1. There is seldom a requirement for respiratory rates in excess of 20
2. Successful recruitment to improve oxygenation will also improve CO_2 excretion.
3. Increasing tidal volume rather than respiratory rate is a more effective initial intervention to reduce CO_2 provided plateau pressures can be maintained below 35cmH$_2$O and inflation pressures (ΔP) less than 20cmH$_2$O.
4. Dynamic hyperinflation should be excluded by:
    a. Ensuring and adequate expiratory time (I:E no less than 1:1.5)
    b. Ensuring expiratory flow and pressure decline to baseline by the end of expiration.
5. Permissive hypercapnia is an acceptable approach for most ICU patients without elevated intracranial pressure.

CONCLUSION

Anaesthesiologists tend to be most happy with respiratory parameters within "normal" limits: oxygen saturations of 98% or more and PaCO$_2$ / ETCO$_2$ 3.5-5.5kPa. Patients in the ICU are able to maintain organ function adequately with saturations of 85-90% and PaCO$_2$s > 8kPa. Further intervention may be doing more harm than good [39].

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