INNOVATIVE PRACTICES ON MECHANICAL VENTILATION

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Introduction

Mechanical ventilation was first introduced during the polio epidemics of the 1950's and since then has been of undoubted value in improving the survival of many patients, including newborns and children. However, problems can stem from its use, particularly if inappropriate ventilatory modes are chosen. This can result in pressure and volume damage to the lungs, haemodynamic instability, oxygen toxicity and nosocomial infection.

Ventilation-induced lung injury (VILI)

Ventilatory modes should be carefully selected to minimise the ventilator-induced lung injury (VILI). The recognition that alveolar overdistension rather than high proximal airway pressure is the primary determinant of the lung injury (i.e., volutrauma rather than barotrauma) has constituted a substantial shift about the patogenesis of ventilator-induced side effects.

Mechanical ventilation with high pressure and volume induces changes in endothelial and epithelial permeability, formation of pulmonary oedema, alterations in pulmonary microvascular permeability. Severe alveolar damage, alveolar haemorrhage and hyaline membranes have been noted in animals that die after lung overinflation injury. The most important factors that have been proposed as responsible for VILI are, firstly, high lung volume associated with elevated transpulmonary pressure and alveolar overdistension, and secondly, repeated alveolar collapse and reopening due to low end-expiratory volume. Other factors that contribute to injury include pre-existing lung damage and/or inflammation, high inspired oxygen concentration, the level of blood flow and the local production and systemic release of inflammatory mediators.

Innovative and protective lung strategies are proposed in order to avoid alveolar overdistension by limiting tidal volume and/or plateau pressure. Lung overstretching and overdistension are significant in causing lung injury rather than high pressures alone; volume trauma is at least as important as barotrauma. Specific and differential lung pathologies should be taken into account with tidal volumes and peak pressures reduced to a minimum. Positive end-expiratory pressure (PEEP) should be used appropriately to maintain alveolar recruitment throughout the respiratory cycle and complementary therapies such as nitric oxide and surfactant used to improve ventilation and oxygenation. Lower end points for ventilation may be accepted, i.e., a PaO_2 of 50-60 mmHg and moderate hypercapnia (45-50 mm Hg). Ventilation should be adapted to changing lung pathology and supportive treatments, such as physiotherapy and prone position, used to improve the lung pathology and to reduce the duration of mechanical ventilation.

CONTINUOUS POSITIVE PRESSURE VENTILATION (CPPV)

Local inhomogeneities of ventilation result in large shear forces applied to lung units undergoing cyclical opening and closing. The repeated collapse and reopening of the lung units at low lung volume may contribute to VILI. A strategy combining recruitment manoeuvres, low tidal volume, and higher PEEP have been demonstrated to decrease the incidence of barotrauma.

Given that appropriate tidal volumes are critical in determining adequate alveolar ventilation and also in avoiding lung injury, volume-control ventilation is the safer and preferable ventilatory mode. Pressure limited ventilation is not indicated in paediatric age and for neonatal ventilation because setting and delivering of specific tidal volumes is not central to the ventilator design. This method has been applied in neonatology due to the simplicity of use.

In volume controlled ventilation, the target tidal volumes (6 mL/kg or lower if necessary) are selected based on ideal body weight. It is adjusted to maintain the pressure-volume curve below the upper inflection point. It should be noted that tidal volume less than or close to total dead space can produce insufficient exchange of alveolar gases (hypercapnia). Using uncuffed endotracheal tubes, a large discrepancy between set and delivered tidal volumes is present. In order to avoid hypoventilation this discrepancy and poor compliance of infant lung compared to the ventilatory circuit compliance must be evaluated.

Respiratory rate has to be adapted to maintain a normocarbia. Generally the specific respiratory rate for the type of patient is increase by 10-15%.

PEEP has to be adjusted to maintain the pressure-volume curve above the lower inflection point, to avoid repeated alveolar collapse and reopening due to low end-expiratory volume, to maintain alveolar recruitment throughout the respiratory cycle. Haemodynamic implications can be reduced maintaining a normal volemia and avoiding high PEEP levels.

PRESSURE REGULATED VOLUME CONTROL (PRVC) VENTILATION

PRVC ventilation is a mode of ventilation now available in newer ventilators. This method delivers a controlled tidal and minute volume in a pressure-limited manner using the lowest possible pressure, which is constant during the inspiratory phase. The gas flow is decelerated and pressure and flow constantly vary, breath by breath, in order to achieve the pre-set tidal volume at minimum peak inspiratory pressure. It is particularly useful in patient ventilated where there are rapid changes in lung compliance and airway resistance, for instance when surfactant and bronchodilators are used.

Methodology

The ventilator tests the first breath at 5 cm H_2O above PEEP and calculates the pressure-volume ratio. The inspiratory pressure changes breath by breath until the preset tidal volume is reached at a maximum of 5 cmH_2O below the set upper pressure limit. At this stage the measured tidal volume corresponds to the preset value and the pressure remains constant. If the measured tidal volume increases above the preset level, inspiratory pressure is reduced until the set tidal volume is reached.

Indications
This mode of ventilation appears to be indicated:
1. if within the lung compliance and resistance vary rapidly;
2. if there is an initial requirement of high flow in order to re-open closed pulmonary areas (e.g. atelectasis, etc.);
3. to reduce high ventilatory peak pressure (e.g. in premature infants, interstitial emphysema, etc.);
4. to control ventilatory pressures from the moment non-ventilated alveoli and bronchioles are re-opened (e.g. surfactant, theophylline or nitric oxide administration, etc.);
5. in the presence of broncho- and bronchiole-spasms (e.g. asthma, bronchiolitis, etc.);
6. in all patients in which PEEP levels must be reduced in order to avoid haemodynamic complications.

Advantages of PRVC ventilation
The method appears to be useful in improving respiratory mechanics and gas exchange, in reducing the barotrauma caused by PIP, in limiting oxygen toxicity due to the possibility of using reduced FiO_2 to maintain adequate gas exchange as compared with conventional mechanical ventilation. The use of decelerating gas flows favours opening of closed areas of the lung and laminar flow which allows the reduction of PEEP levels in case of haemodynamic implications. It appears also beneficial when drugs such as surfactant, bronchodilators, nitric oxide, etc., which bring about a rapid change in compliance and airway resistance, are used.

Clinical controlled trials are required to evaluate the benefits of PRVC ventilation in the acute phase of lung pathology, in ventilation of healthy lungs (i.e., neurosurgical patients) and during weaning from ventilator.

VOLUME SUPPORT VENTILATION (VSV)

VSV is a new means of assisting spontaneous breathing which avoid the disadvantages deriving from pressure support ventilation. The ventilator, breath by breath, adapts the inspiratory pressure support to the changes in the mechanical properties of the lung and the thorax in order to ensure that the lowest possible pressure is used to deliver the pre-set tidal and minute volume that remain constant. The inspiratory pressure is constant and the flow is decelerated. When the patient is able to ventilate the pre-set tidal volume, the ventilator does not support the single breath. At this stage, extubation may be performed with safety. In cases of apnea the ventilator automatically switches to PRVC. The initial values for expected tidal and minute volume should be set as should all parameters to be used in PRVC in the presence of apnea ventilation.

Indications
Intensive care
1. weaning from short and long term ventilation;
2. weaning of patients with chronic obstructive pulmonary disease e.g. infants with severe bronchopulmonary displasia (BPD);
4. to promote respiratory muscle training in critically ill patients;
5. to compensate for the high resistance of endotracheal tubes during spontaneous breathing and CPAP.

Postoperative care
1. to preserve or reactivate spontaneous breathing;
2. to reinflate areas of collapsed or atelectasic lung after surgery.

Contraindications VSV:
1. use of deep sedation and muscle relaxants;
2. central neurological disorders;
3. small premature infants who may be unable to trigger the demand valve.

PERMISSIVE HYPERCAPNIA

A lung protective strategy may lead to CO2 retention. Tidal volume can be limited so that the physiologic dead space fraction for each breath rises to the point at which frequency cannot be increased to normalize effective alveolar minute volume. Hypercapnic acidosis has to be avoided as it is associated with decreased myocardial contractility, cerebral vasodilation, decreased seizure threshold and hyperkalemia. Moderate CO_2 retention, if compensated and allowed to develop gradually, can be well tolerated. It has been suggested that hypercapnia be limited to a degree that allows arterial pH to be maintained >7.2.

Investigation into the effects of hypercapnia on tissue oxygenation indicates increased cardiac output, reduced arterio-venous content difference, and reduced lactate production. Permissive CO2 retention is contraindicated in increased intracranial pressure and in pulmonary hypertension.

Further definition of patient groups in whom hypercapnia is poorly tolerated will be important in the formulation of general recommendations regarding the use of these ventilatory strategies.

PRONE POSITIONING

In acute lung injury a gradient in regional compliance develops favouring non dependent lung. In addition, due to an increase in lung mass, there is an accentuation of the normal gradient in pleural pressure which increases as one approaches dependent lung.

In supine position, the lowest regional end-expiratory volumes and the greatest frequency of cyclic airspace collapse and recruitment is found in dorsal lung. By rotating the patient to the prone position, the least compliant lung with the most favourable transalveolar pressure excursion and limit tidal transalveolar pressure change are present in ventral lung regions.

The increased dorsal lung recruitment and ventilation, rather than a significant redistribution of regional blood flow, improves oxygenation and ventilation/perfusion matching, and reduces shunt in patients with lung injury in several uncontrolled studies: The improvement in compliance that occurs in the prone position may allow reductions in FiO2 and PEEP and augment drainage of secretions from dependent lung.

Safety concerns, including accidental extubation and catheter removal, haemodynamic instability and pressure necrosis can limit the application of the prone position.

HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV)

High-frequency ventilation (HFV) has been one of the most studied ventilation techniques over the past two decades. Despite its theoretical benefits it has not received unanimous consensus and has not been widely used.

The most fundamental difference between high frequency ventilation (HFV) and intermittent positive pressure ventilation (IPPV) is that with HFV the tidal volume *(Vt)* required is approximately 1-3 ml kg/body weight, compared with 6 10 ml with IPPV. The increase in ventilation rate to frequencies of 60 b.p.m. or more in HFV is obviously mandatory if even comparable minute volume ventilation is to result.

Three models are currently under investigation: High-frequency positive pressure ventilation (HFPPV), high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV). The first two are no longer used in intensive care therapy due to their poor results in trials compared to conventional mechanical ventilation. HFJV has found an important place in tracheobronchial surgery. HFOV is proving highly successful, mainly because adequate equipment capable of solving the problem of humidification of ventilated gases is now available.

High Frequency Positive Pressure Ventilation. Tidal volume is delivered via a normal sized tracheal tube with inspiration being the only active part of the ventilatory cycle (i.e. expiration achieved by passive lung recoil). Frequencies are usually in the range 60-120 c.p.m. (1-2 Hz).

High Frequency Jet Ventilation. Tidal volume is delivered via a narrow cannula or injector resulting in a jet of high velocity gas, normally at frequencies of 60-600 c.p.m. (1-10 Hz).

High Frequency Oscillation. Tidal volume is delivered via normal sized tracheal tubes and both inspiration and expiration are active and of approximately equal power, such as would occur with an oscillating piston or loudspeaker-based ventilator. Frequencies range from 2 Hz to more than 100 Hz (6000 c.p.m.).

High Frequency Oscillation (HFO)
The ventilator is usually a reciprocating pump of the piston variety or a loudspeaker system driven by an electronic oscillator. Both systems generate a sinusoidal respiratory flow pattern. From this, it follows that the I:E ratio is usually fixed at 1:1, although variable-ratio pumps have recently been described. The pomp is used to produce a reciprocating flow in the airways, whilst an auxiliary gas flow - bias flow -, is used to clear the extracted carbon dioxide and to provide fresh gases to the system. These systems behave as a T-piece circuit, and the efficiency of carbon dioxide removal is a function of the magnitude of the bias flow.

There are a number of mechanisms proposed to explain the gas exchange in HFOV. Direct alveolar ventilation, asymmetric velocity profiles, Taylor dispersion, pendeluft, cardiogenic mixing, accelerated diffusion and acoustic resonance appear to participate in gas exchanges both individually and/or together.

Clinical considerations
Gas trapping
This problem assumes increasing importance as the ventilatory frequency increases and if the expiratory time is reduced to less than 250 ms. The shorter the expiratory period and the

greater the respiratory time constants, the lower the frequency at which gas trapping becomes a problem. A modest degree of gas trapping is not always undesirable, and the term “auto-PEEP” may give a more balanced view of this effect. Gas trapping is less likely to occur in HFOV systems in which expiration is assisted. If the conducting airways were rigid structures this might be true, but in reality the airways are more likely to dose as a result of the negative pressure phase, with increased gas trapping and reduction of ventilatory efficiency.
The proximal airway pressure is not a real indicator of true intrathoracic pressure during HFOV, and oesophageal pressure may be a better index for clinical use.

Humidification during HFOV
Humidification of the fresh gas flow during HFOV is at present not a problem. The need for good humidification in HFOV is paramount. The fresh gas flows required in HFOV can easily exceed 30 litre min-1. Even 75 % humidification would mean that the drying effect on the respiratory tract would be the equivalent of 7.5 litre of dry gas each minute. Early attempts to overcome this problem used a conventionally humidified low pressure gas stream which was entrained by the jet injector. The final gas mixture would at best be only 75 % saturated and, in patients with reduced pulmonary compliance, this figure could decrease to as little as 10%. Clearly, those systems that rely on entrainment cannot be used clinically for more than the briefest period of HFV.

Cooling effects of HFV
There is no documented evidence for such a claim, provided that adequate humidification is provided. The gas flows used in HFOV may be high, but the thermal capacity of gases is very low. In contrast, the latent heat of vaporization of water is considerable. In HFJV for example, at typical clinically used minute volumes, the cooling effect from the gas alone is the equivalent of about 250 $kCal^{-1}$ about 7-10% of the daily calorie requirement. The cooling effect that would result from the use of dry gas, with the consequent latent heat losses from evaporation, would be approximately 3000-3500 kCal day^{-1}. Thus simple warming of the inspired gas would produce little clinical benefit.

Prevention of aspiration
It has been claimed that high frequency ventilation prevents aspiration of pharyngeal contents by virtue of its “auto-PEEP” effect. While this is largely true in paralysed, anaesthetized patients, those who are capable of voluntary inspiration or coughing can still generate a negative tracheal pressure which could result in aspiration.

The theoretical <u>advantages</u> of HFOV include maintaining the airways open; smaller phasic volume and pressure change; gas exchange at significantly lower airway pressures; less involvement of cardiovascular system; less depression of endogenous surfactant production. HFOV is recommended in order to reduce lung barotrauma and consequent lung injury in non homogeneous lung pathology, in air leaks, in Persistent Pulmonary Hypertension of the Newborn (PPHN) and in the ventilation of premature babies.

<u>Contraindications</u> of HFOV are in case of pulmonary obstruction from fresh meconium aspiration, bronchopulmonary dysplasia and RSV bronchiolitis and in case of intracranial haemorrhage.

The described <u>complications</u> of HFOV are connected with overinflation in obstructive lung diseases, intracranial haemorrhages, reduction in heart rate attributed to increased vagal activity, bronchopulmonary dysplasia, necrotising tracheobronchitis, increased permeability of lung epithelium and insufficient humidification of tracheo-bronchial secretions.

While HFOV can maintain adequate gas exchange for prolonged periods in many situations, there is as yet no clearly defined clinical role for this mode of ventilation. Recent studies in premature babies with hyaline-membrane disease and in term or near-term hypoxemic newborns have demonstrated an important improvement in oxygenation and a reduced incidence of air leak with HFOV. There is limited published data on the use of HFOV in paediatric patients but from it the benefits deriving from the re-opening of the closed alveoli and maintaining them open, as well as reduction of air leak, have to be demonstrated.

There are no data from randomized controlled trials supporting the routine use of rescue HFOV in term or near term infants with severe pulmonary dysfunction. Cochrane Review (November 2000) showed no evidence of a reduction in mortality at 28 days, in number of patients requiring extracorporeal membrane oxygenation, days on a ventilator, days in oxygen or days in hospital. A large-scale trial has recently confirmed this data and showed a greater incidence of pulmonary air leak during the course of the study.

Despite the absence of any clearly defined clinical niche for HFOV, there seems little doubt that it will continue to be used extensively in bench testing and animal experimentation.

INDEPENDENT LUNG VENTILATION (ILV)

In infants with lung injury, the affected lung presents reduced compliance and greater respiratory airway resistance than the less affected lung. When these infants are mechanically ventilated, the ventilated gases are preferentially deviated towards the less pathological lung, thereby over-expanding it and providing little benefit for the more affected lung. The result is that the affected lung receives insufficient ventilation while the less affected lung could be over ventilated, defeating the purpose of mechanical ventilation. Similarly, the application of positive end-expiratory pressure (PEEP) would increase in the thoracic compliance in the more compliant lung and a smaller share of Tidal Volume (TV) for the less compliant lung. An accentuated increase of TV in one lung may result in a greater mismatching of alveolar ventilation (VA) and perfusion (Q). Further, this may lead to the development of iatrogenic lung diseases, i.e. alveolar ruptures, interstitial emphysema and bronchopulmonary dysplasia (BPD).

The possibility of separate ventilation of the lungs of newborn and children by means of selective intubation was first reported in 1984, using two single tubes. Despite favourable results the method itself was complicated and difficult to apply. A notable change occurred with the testing and clinical use of a prototype bilumen tube, later manufactured by Portex Ltd. The arrival of this tube, in addition to simplifying the intubation manoeuvre and facilitating nursing, has made it possible to apply independent lung ventilation to the treatment of unilateral lung disease in paediatric age. The method has also been used in the treatment of intra-operative and post-operative disorders in children who have undergone thoracic surgery and whenever different ventilation and /or a different PEEP level to each lung are required.

Selective bronchial intubation

Over 6-8 years of age, selective bronchial intubation is possible using a cuffed double-lumen tube similar to that used in adults (26-28 Fr. Bronchocath Mallinckrodt®, Bronchoport

Rusch®). The Marraro Paediatric Endobronchial Bilumen Tube , produced by SIMS - Portex®, may be used in neonates and children 2-3 years of age. It is uncuffed to maximize the internal diameter of the tube and has no carinal hook, thus minimizing tracheal trauma.

Ventilators

ILV requires the use of two synchronisable ventilators for the start of each breath, but which permit the application of different modes of ventilation to each lung. Synchronisation avoids mediastinal shifts which would otherwise reduce venous return and cardiac output. Furthermore, non-synchronous ventilation of the lungs may encourage the appearance of serious ventilation disorders. These complications occur mainly at respiratory frequencies less than 30 breath per minute. A prototype flow-deviator is under experimentation in order to test the possibility of using only one ventilator during ILV. The use of one ventilator can simplify the application of ILV and can reduce the costs.

Method of application of ILV

The initial tidal volume for each lung is calculated by halving that used during conventional ventilation (air leaks and resistance of the tube should be taken into account). Appropriate *Vt* for each lung is decided taking into account the lung pathology and compliance and the resistance offered by the tube. The resistance of the bilumen tube, especially the longer bronchial branch, is greater than conventional tubes. Adequacy of ventilation is assessed after an hour and then at 3-4 hourly intervals until the patient is stable. Once stable, 8 hourly assessments of the patient are adequate, with modification of inspired oxygen tension and ventilator settings, including PEEP, as appropriate. It is recommended that ILV is only discontinued after definite improvement in blood gases and clinical and radiological parameters are seen. Discontinuing treatment too soon risks losing benefits gained.

Haemodynamic impact of ILV

The haemodynamic changes with ILV are similar to those encountered with intermittent positive pressure ventilation - IPPV - with 5 cmH_2O PEEP. If levels of PEEP are too high or tidal volume too great, central venous pressure rises and heart rate and blood pressure fall. Higher levels of PEEP may be maintained without haemodynamic complications in the worse affected lung than the normal lung.

Variations of gas exchange

Application of PEEP allows recruitment of small airways, re-expansion of alveoli and improvement in oxygenation and carbon dioxide elimination. Using a bilumen tube, best PEEP for each lung may be applied.

Advantages of ILV:

1. functional residual capacity and ventilation are increased preferentially in the more damaged lung;
2. hyperventilation and consequent barotrauma is reduced in the less damaged lung;
3. differential levels of PEEP may be used in each lung;
4. secretions may be isolated in one lung, reducing overspill infection in the other lung.

Indications for ILV

<u>In respiratory disease in intensive care:</u>

1. treatment of unilateral atelectasis, emphysema and pneumonia;
2. treatment of lung pathology complicated by atelectasis, pneumothorax or fistula.

In cardiothoracic surgery:
1. re-expansion of the collapsed lung at the end of operation.

In post-operative intensive care:
1. lung re-expansion after cardiac surgery;
2. correction of V/Q mismatch of dependent lung;
3. treatment of pulmonary complications e.g. pneumothorax or aspiration syndromes.

Possible new indications for ILV are:
1. intensive care treatment of patients with bilateral mixed pulmonary pathology. In bronchopulmonary dysplasia patchy areas of emphysema may compress adjacent areas causing atelectasis, especially in the first 6 months of life;
2. selective administration of drugs to one lung, such as antibiotics or surfactant. The benefits of ILV may be improved by the selective administration of surfactant.

Unsolved problems remain:
- the application of PEEP is limited due to the development of large air leaks;
- it is difficult to humidify and warm inspired gases. The lumens of the double tube are small and easily blocked by secretions;
- at present the operating costs are high as two ventilators are required. A reduction in the time spent in intensive care may produce cost savings so as the future use of the flow-deviator and only one ventilator.

TOTAL AND PARTIAL LIQUID VENTILATION USING PERFLUOROCARBONS

The possibilities of using liquid instead of air in the exchange of gases became reality with the discovery of the properties of perfluorocarbons (PFC). In 1963 Clark demonstrated that mice, rats and other animals can survive after immersion in oxygenated PFC and thus opened the way to current clinical research and applications .

Characteristics of Perfluorocarbons
PFC are derived from common organic compounds such as benzene. They are colourless and odourless, and can be stored indefinitely at room temperature. They are resistant to autoclaving. They are insoluble in water or in lipids and water or lipids do not dissolve in them. Oxygen, carbon dioxide and many other gases are very easily dissolved in them. All PFCs have a low surface tension and rapidly evaporate at body temperature.

There are a number of PFCs in clinical use. Properties of selected PFCs are compared with water below.

	Water	Rimar 101*	Perflubron**	FC77***
Boiling point (°C)	100	101	143	97
Density at 25°C (g/ml)	1.00	1.77	1.93	1.75
Kinematic Viscosity (centistokes at 25°C)	1.00	0.82	1.10	0.66
Vapor pressure (mm Hg at 37°C)	47	64	11	75
Surface tension	72	15	18	14
O2 solubility at 37°C (ml gas/ 100 ml liquid)	3	52	53	56
CO_2 solubility at 37°C (ml gas / 100 ml liquid)	57	160	210	198

* Rimar® 101 from Mitsubishi, Milano, Italy
** Perfluoroctylbromide (Perflubron®) from Alliance Pharm. Corporation, San Diego, California, USA.
*** FC77® from 3M Corporation, St. Paul, Minnesota, USA.

PFC spontaneously evaporates from the lung and the skin. The mechanisms for uptake, distribution and elimination in the body are not clearly defined but are correlated to lipid tissue composition, organ perfusion and ventilation-perfusion ratio in the lung. The physiochemical characteristics of the PFC, i.e. molecular structure and vapour pressure, and lung pathophysiology play an important role. Small quantities of PFC can be absorbed in the blood and distributed to the tissues with preference for lipids and fats. The PFC absorbed can remain in the tissues for long periods but does not seem to exert any toxic effects. The persistence in the body and the predilection for fatty tissue warrants further investigation, particularly with respect to the developing central nervous system of neonates and premature babies.

The development of applications of liquid ventilation
The first use of oxygenated PFC was for total immersion but subsequently it was used in bronchoalveolar lavage in order to maintain gas exchange during the manoeuvre and remove foreign material from the lungs. A significant advance in the application of liquid ventilation was the introduction and elimination of liquid from the lung by gravity, by lying the subject in a suitable position. The design of the demand-regulated ventilator by Moskowitz in 1970 and its subsequent simplification by Shaffer, has led to more widespread clinical use of PFCs. At present, there are two methods of administration of PFCs. Total Liquid Ventilation (TLV), developed by Shaffer et coll. and Partial Liquid Ventilation (PLV) or Perfluorocarbon Associated Gas Exchange (PAGE) proposed by Fuhrman's and Lachmann's groups.

Total Liquid Ventilation (TLV)
TLV is a ventilatory technique employing PFCs instead of gas to obtain gas exchange. It requires complex equipment (pump, membrane oxygenator, CO_2 removal, etc.) and is applied after a short period of partial liquid ventilation. The lungs are gradually filled with warmed oxygenated PFC. A volume of 30 ml/kg of PFC is introduced and further quantities are administered until the lung has been completely filled. As soon as the air has been completely expelled, the patient is connected to a ventilator (similar to a dialysis pump). Tidal volume is subsequently set at 15-20 ml/kg of PFC. Respiratory rate is regulated to 4-5 breaths per

minute in order to obtain better CO_2 elimination. The maximum inspiratory peak pressure is 30 cm H_2O but a pressure of between 15 and 20 cmH_2O is usually sufficient. The negative pressure required during the expiratory phase ranges from $^-15$ to $^-30$ cm H_2O. At the end of the treatment conventional ventilation can be continued until the PFC has evaporated from the lung.

<u>Partial Liquid Ventilation (PLV)</u>

PLV is a ventilatory technique employing PFCs to fill the functional residual capacity () of the lungs whilst gas tidal volumes are delivered by a conventional volume-regulated ventilator. A volume of 30 ml/kg of PFC is introduced in order to partially or fully replace the FRC. A further 10 ml/kg of PFC is added every hour to replace redistribution or evaporative losses.

Clinical considerations

A persistent problem noted in early use of PFCs was a significant degree of lactic acidosis. A fall in cardiac output has been noted, possibly linked to an increase in pulmonary vascular resistance due to the compression of the pulmonary vessels by the heavier liquid. Intravascular volume expansion with colloid has been used in order to minimise the haemodynamic changes.

CO_2 elimination is linked to the persistence of the PFC in the lung and dead space. Whilst PFC readily absorbs CO_2, it does not allow its rapid diffusion. During TLV, PFC is highly viscous and dense and thus a very low frequency ventilatory rate is necessary to eliminate an accumulation of CO_2 and respiratory acidosis. In animals the most effective alveolar ventilation and CO_2 elimination occurs at frequencies of 3-5 breaths per minute, whilst in humans the most effective rate appears to be 4-5 breaths per minute.

Adequate oxygenation is achieved by manipulations of the FiO_2 of the inspired liquid and by maintaining an adequate FRC by varying inspiratory and expiratory volumes and PEEP level. In animal and preliminary human studies, TLA and PLV are very effective in improving oxygenation. Unlike the gas-filled lung, in which alveolar pressures are uniform and vascular pressures are subject to a hydrostatic gradient, the liquid-filled lung has transmural gradients that are relatively balanced. These results in uniformly distended pulmonary blood vessels and evenly distributed blood flow, thus improving ventilation-perfusion matching. The haemodynamic implications during PLV are less evident than during TLV. In areas of atelectasis, ventilation-perfusion matching and decreased pulmonary resistance through the lung appears to lead to recruitment and unfolding of alveolar tissue and capillaries.

The improvement in gas exchange and the increase in compliance could indicate more effective oxygenation and ventilation, presumably because of a reduction in alveolar surface tension. Any material present in the lung could be mobilised and eliminated and therefore these re-ventilated areas can be recruited to ventilation.

Peak inspiratory pressure is lower during liquid ventilation compared to conventional gas ventilation. The incidence of barotrauma and alteration of lung structure is thus reduced. This observation has been confirmed in an experiment where 10 guinea pigs were treated with diluted human meconium. In four of these, the lungs were subsequently washed with saline solution and conventionally ventilated. The other 6 were washed three times with PFC and conventionally ventilated. In the first group there was considerable damage to the entire lung structure and particularly to the terminal bronchioles and alveoli which were full of meconium

The liquid ventilated group however showed no signs of damage to the lungs and no traces of meconium were found in either the bronchioles or in the alveoli .

Advantages of PLV over TLV
1. PLV uses the same equipment as for conventional mechanical ventilation. TLV requires the use of specialised equipment.
2. There is greater cardiovascular stability using PLV.

Indications for liquid ventilation
It has been supposed that liquid ventilation eliminates the air-liquid interface and reduces surface tension. For this reason it has been tested in Respiratory Distress Syndrome (RDS) in premature babies and Acute Respiratory Distress Syndrome (ARDS) in children and adults.

Unfortunately, preliminary clinical trials on newborns and children were interrupted due to incorrect protocol of treatment and disappointing initial results. A clinical trial conducted in the United States and Europe, involving 56 Centres, on 311 adult patients affected by ARDS from different origins was disappointing on the beneficial effects of PLV versus conventional ventilation. Two different dosages of PFC were tested. Mortality was higher in patients treated with PLV. Moreover, severe hypoxemia developed in presence of inhomogeneous lung patology due to the compression of pathologic areas and normal areated lung units. The incidence of pneumothorax was higher and return to conventional ventilation was more difficult than previously supposed. However, the PFC used was demonstrated to be safe.

Even though the results on ARDS were disappointing, other fields of research remain open and are being thoroughly investigated. For example, PFC-BAL may be useful in meconium aspiration and inhalation syndromes where it facilitates the removal of the meconium or other material present in the lung, supports gas exchanges and eliminates dishomogeneous lung ventilation. Future applications could be in the treatment of cystic fibrosis and proteinosis. In both cases PFC could remove the material present in the lungs, improve gas exchange, reduce the tendency to atelectasis and prevent the loss of surface activity. Should the afore-mentioned be confirmed by large clinical trials.

Liquid ventilation is also investigated for the study of the lung structure, in radiology, for topical administration of drugs e.g.antibiotics and chemotherapics, heating pulmonary lobi to increase haematic flow in the treatment of lung cancer and as a ventilatory support for unusual types of treatment.

Several problems remain to be solved:
- the safety of liquid ventilation over prolonged periods of time and return to conventional gas ventilation;
- the haemodynamic effects in the presence of pulmonary hypertension;
- the significant degree of lactic acidosis and the increase in hypoxemia in inhomogeneous lung pathology;
- the uptake and metabolism of PFC with regard to damage from long term persistence in the tissues.

Liquid ventilation in its various possible applications is a fascinating and stimulating area requiring further study. In order to avoid disappointment following the initial enthusiasm, widespread clinical trials must confirm its applicability and positive results in humans.

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