INTRODUCTION

ARDS (Acute Respiratory Distress Syndrome) refers to a group of pathological conditions described by severe hypoxia, severe lung inflammation and oedema, and reduced lung compliance. The syndrome carries a high risk of death (> 30% in 2004), often associated with multiple organ failure, sepsis, trauma or surgery.

Whilst an effective therapeutic approach against the underlying aetiology is of the utmost importance for ultimate survival, supportive therapy is certainly a key element in achieving both short and long term survival.

Our aim in this brief discussion is to present some of the recent developments in the field of ventilatory support, which is the essential element in the supportive management of patients with ARDS.

GOALS OF MECHANICAL VENTILATION

Mechanical ventilation was introduced in the 1950’s to substitute for the absent or decreased respiratory muscle function in patients paralyzed by Polio infection. It soon became the basis of Intensive Care, and its use spread to most acute respiratory failure conditions.

While being designed to provide the mechanical power for breathing and hence CO₂ elimination in patients unable to achieve it on their own, mechanical ventilators have become very important and convenient tools to manage hypoxaemic patients with ARDS. Ventilators provide easy control of the inspired oxygen fraction, airway pressure and, possibly, alveolar recruitment.

Mechanical ventilation has become the main supportive technique for most Acute Respiratory Failure patients. Mechanical ventilation saves lives, but as for most therapies we have learned to recognize its risks and side effects.

VENTILATOR INDUCED AND VENTILATOR ASSOCIATED LUNG INJURY

As early as 1967 Nash [1] reported on pulmonary lesions associated with oxygen therapy and artificial ventilation. A lot of experimental and clinical data followed, clearly showing that mechanical ventilation, as practiced up to the late 90’s, can lead to severe lung damage, mimicking the lung pathology typical of ARDS itself. These severe side effects appeared to be related to the use of Tidal Volumes in excess of 10 ml/Kg, low respiratory rates and variable amounts of end expiratory pressure. When the National Institute of Health (NIH) sponsored the ECMO trial [2], it was hoped that extracorporeal gas exchange could provide time for the lung to rest and heal. Unfortunately the trial was unsuccessful, but, when analyzed in retrospect, lung management did not differ much in terms of tidal volumes, respiratory rates and even airway pressures. This might have been indeed one of the main reasons contributing to the NIH ECMO trial failure. The notion that mechanical ventilation can in itself damage the lung evolved from the concept of gross barotrauma to volotrauma, and then to the one of biotrauma. The latter term implies in short that mechanical ventilation can cause an inflammatory response in the lung, that then spreads to the entire organism through the release of mediators, finally causing multiple organ failure and death [3].

It has been recently shown that patients not affected by Acute Lung injury (ALI) but undergoing mechanical ventilation do develop acute lung injury more frequently when ventilated with high rather than with low tidal volumes [4], providing additional clinical evidence for the concept of ventilator induced lung injury.
LOW VS HIGH TIDAL VOLUMES

In 1979 we reported the first clinical application of extracorporeal CO₂ removal, a technique aimed at providing a complete dissociation between the lung ventilatory management and gas exchange [5]. By providing extracorporeal CO₂ removal, the natural lung can be ventilated at any rate and tidal volume, down to complete apnea. The technique, requiring extracorporeal circulation and the application of an artificial membrane lung is technically complex and requires expert and costly management, restricting its use to a few institutions. The concept of lung rest and avoidance of ventilator induced lung injury led Hickling [6] to develop the simple and effective concept of permissive hypercapnia: the achievement of normal Pa CO₂ levels is not necessary in ARDS patients, and therefore minute ventilation and peak airway pressures can be limited, provided the patient can tolerate moderate to high levels of hypercapnia. The possibility that by limiting tidal volume and airway pressure the survival of ARDS could be improved stimulated the NIH funded “ARDSnet” group of investigators to design a study explicitly devoted to verify whether low tidal volumes (6 ml/kg ideal body weight) could provide a survival advantage compared to standard (i.e. 12 ml/kg) tidal volumes [7]. The study provided for the first time strong evidence from a Randomized Clinical Trial that the way we ventilate patients can change survival, and that high tidal volumes are dangerous.

In the same year Amato [8] published a smaller trial comparing a protective (i.e. low tidal volume + permissive hypercapnia) ventilatory strategy with the traditional high tidal volume strategy. In this case too the difference in survival was impressive (62% versus 29%). An important difference between the Amato and the ARDS net study was in the use of Positive End Expiratory Pressure (PEEP).

While the PEEP level in the treatment arm of the “ARDSnet” group averaged little more than 9 cm H₂O, it amounted to more than 16 cm H₂O in the treated arm of the Amato study. Can we compare the ARDSnet lung protective strategy with the one of Amato? Ample evidence is available to favour the Amato approach: Webb and Tierney in 1974 had already showed that PEEP protects experimental animals from barotrauma [9], while Muscedere [10] showed in isolated lungs that PEEP high enough to prevent end expiratory collapse could protect from ventilation associated lung damage.Gattinoni [11], using CT scan, showed in ARDS patients that, unless a high enough PEEP is provided, the lungs undergo cyclical opening at end inspiration and closing at end expiration. Using a PEEP high enough to keep open the airways recruited during inflation became a target of the ventilatory strategy. Fortunately enough, even in ARDS lungs, the pressure needed to reopen recruitable alveoli is higher than the pressure at which they close down. Unfortunately though, opening pressures as well as closing pressures differ between individual alveoli, so that a distribution can be described rather than a single critical value, and we must make compromise choices in selecting PEEP values.

The “ARDSnet” designed indeed a study (called the ALVEOLI study [12]) to compare two lung protective low tidal volumes strategies, one using high PEEP (average 12cm H₂O) and the other low PEEP (8 cm H₂O). Unfortunately the study suffered from some drawbacks in the protocol design, which had to be changed halfway, probably from too small a difference in PEEP, and certainly from bad luck, since the treatment arm enrolment was biased by a higher age and higher severity of the disease. So the ALVEOLI study is unfortunately non conclusive, but, at least, it shows that a PEEP strategy such as the one used in the treated arm is not harmful compared to the control.

NEGATIVE EFFECTS OF THE LOW TIDAL VOLUMES

ARDS affected lungs have a strong tendency to collapse. While it has not been proven that alveoli heal better when open than when collapsed, it is certain that gas exchange is better in a recruited lung, and that the worse situation is the one in which airways open during inspiration and collapse during expiration. Low tidal volume strategies carry the risk of fostering lung collapse in a very unstable lung. This risk is real even in normal lungs, which require periodical sighing to maintain optimal recruitment, both during spontaneous physiological breathing and artificial ventilation (anaesthesia). An additional mechanism favouring collapse is given by the high FiO₂ used in ARDS patients: absorption atelectasis is a real risk, made even more probable by the severe VA/Q maldistribution typical of the syndrome. However we have no information available about the interplay between airway pressure, FiO₂, and lung mechanics on the occurrence of absorption atelectasis. We showed however that when using low tidal volumes, particularly with pressure control ventilation, a progressive lung collapse may take place over a short time, leading to a decrease in lung compliance. This effect is counteracted by an increased PEEP [13].
Therefore, while in the 70’s the lungs were kept open and recruited by high end inspiratory pressures, low tidal volume ventilatory strategies brought back the need for recruitment manoeuvres and recruiting strategies. Lachmann developed the concept of the “open lung strategy”, while many different recruitment manoeuvres may be applied. Examples of them can be found in the studies by Lapinsky [14] and Amato [8]. Certainly the effects of recruitment manoeuvres can be seen only if a high enough PEEP is applied after the manoeuvre to maintain the effect, and if, conversely, PEEP and/or Tidal Volumes are low enough to make the effect of the recruitment manoeuvre noticeable. So it is entirely possible that, given the appropriate experimental conditions, recruitment manoeuvres provide no measurable advantage.

An alternative solution is proposed by cyclical (0.5 to 4 times per minute) recruitment manoeuvres provided automatically by the ventilator in the form of sighs or “deep breaths”. We, as well as others, have shown the beneficial acute effects of sighs in both controlled and assisted breathing [15].

**PRONE POSITIONING**

Sick adult patients are normally nursed in a supine or semirecumbent position, even if this position is not the one physiologically adopted by normal subjects e.g. during sleep. The improvement in oxygenation attained by positioning ARDS patients prone is a common observation, the mechanism of which has been extensively investigated. A large clinical trial conducted in Italy [16] in over 300 patients was unable to show a positive effect of prone positioning upon survival, in spite of an improvement in oxygenation. In a post hoc analysis, the study suggested a possible beneficial effect in the sub group of the most severely affected patients. A second large French study [17] was also unable to show any beneficial effect upon survival, it raised some safety issues, and proved a decreased incidence of Ventilator Associated Pneumonia (VAP) in the prone group. In conclusion, while prone positioning achieves better oxygenation and decreases the incidence of VAP, its effect upon survival, at least in the general population of ALI/ARDS patients is still unproven.

**PREVENTION OF VENTILATOR ASSOCIATED PNEUMONIA**

VAP is a common complication of ARDS, often contributing to the development of sepsis, multiple organ failure, and death. The problem of its prevention is central to the ventilatory management of these patients [18].

The semirecumbent position is recommended as the one that minimizes the risk of bacterial inhalation in intubated, mechanically ventilated patients. While this might be true, we are intrigued by a recent publication suggesting that the semilateral position may be the best to prevent VAP, by keeping the endotracheal tube horizontal rather than elevated as currently recommended [19].

The endotracheal tube inner surface constitutes an ideal culture medium for bacteria, that can grow at 37°C in a humid atmosphere, in a location where antibiotics will never get to. Bacteria will grow in a biofilm, positively interacting and profiting from the presence of a mucous matrix deposited over the tube’s internal surface. To prevent bacterial amplification and continuous bacterial inhalation from the endotracheal tube, Berra et al proposed [20] the coating of the endotracheal tubes with antiseptics to effectively decrease bacterial colonization of the ventilator circuit, lungs, and endotracheal tube itself.

**CONCLUSIONS**

Ventilatory strategies can affect survival: it has been definitely proven that high tidal volumes yield a lower survival rates than smaller ones: a tidal volume of 6 ml/Kg ideal body weight is now recommended as the best available choice. We have reasons to believe that a strategy that maintains an “open lung” rather than a collapsed one is beneficial: the best strategy for PEEP selection, recruiting manoeuvres and/or sighing still remains to be defined. New experimental indications for the prevention of VAP are very promising, and warrant clinical testing.
REFERENCES


