Carbon dioxide dialysis will save the lung

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Mechanical ventilation and ventilator-associated lung injury could be avoided by decreasing the ventilatory needs of the patient by extracorporeal carbon dioxide removal. The reasons for the increased ventilatory needs of the patients with acute respiratory distress syndrome are outlined, as well as some of the mechanisms of continuing damage. Extracorporeal gas exchange has been used mainly as a rescue procedure for severely hypoxic patients. Although this indication remains valid, we propose that extracorporeal carbon dioxide removal could control the ventilatory needs of the patient and allow the maintenance of spontaneous breathing while avoiding intubation and decreasing the concurrent sedation needs. A scenario is depicted whereby an efficient carbon dioxide removal device can maintain blood gas homeostasis of the patient with invasiveness comparable to hemodialysis. High carbon dioxide removal efficiency may be achieved by combinations of hemofiltration and metabolizable acid loads. (Crit Care Med 2010; 38[Suppl.]:S549–S554)

KEY WORDS: ventilator-associated lung injury; gas exchange; mechanical ventilation; hyperventilation; hemofiltration

We contend that mechanical ventilation (MV), although a life-saving procedure, is marred by many serious side effects substantially contributing to morbidity and mortality, and that extracorporeal CO_2 removal, being able to decrease the patient's need for ventilation, has the potential to avoid entirely MV side effects and to contain substantially its use in the intensive care unit.

Mechanical Ventilation: A Life-saving Procedure That Can Kill the Lung

One of the most important missions of intensive care is to substitute the function of failing organs and systems by applying techniques and devices designed to maintain the body homeostasis despite the pathophysiological derangement. Artificial organs are part of such therapeutic armamentarium. When the kidney fails, we apply an artificial kidney to maintain water and electrolyte equilibrium, as well as to remove the toxic metabolites normally excreted by urine. Far more common is the application of another artificial extracorporeal organ: the mechanical ventilator. The mechanical ventilator was originally designed to substitute the respiratory muscle function, because it is designed to move air in and out of the lung of a patient unable to provide the required respiratory work. A typical everyday example of its application is found in any surgical theater, where pharmacologically paralyzed patients are ventilated artificially to avoid apneic death during surgery. Mechanical ventilators (once called artificial respirators) are effective when used to their proper goal. Since the Copenhagen Polio epidemic of 1952 (1), MV has extended from the operating theater to specialized wards of the hospital, giving birth to modern intensive care units.

From then on, the availability of MV and the outstanding experience intensive care unit anesthesiologists had achieved with it made its application to acute and chronic respiratory failure (or distress) a natural, although not entirely rational, step. In the same years, the notion that premature neonates affected by infant respiratory distress syndrome could benefit from continuous positive airway pressure (2) led to the broad diffusion of positive end-expiratory pressure and continuous positive pressure ventilation in patients with acute respiratory failure.

However, we should consider how MV is far from being the ideal tool to care for diseased lungs. If we take acute respiratory distress syndrome (ARDS) as the paradigm of the mechanically ventilated patient, then we should first of all recognize how oxygenation has no direct relation with ventilation. It depends mostly on the inspired oxygen fraction and on airway pressure, the control and application of which are achievable without the mechanical ventilator (continuous positive airway pressure is a good example of this).

MV is applied to maintain adequate ventilation, i.e., CO_2 elimination, in a patient with acute lung injury/ARDS who is handicapped by unfavorable lung mechanics and increased ventilatory needs. This combination makes MV an effective relief of the patient's respiratory distress.

But at this point of the discussion, it will be sufficient to recognize how MV directly controls CO_2 elimination by providing a minute ventilation that the physician can increase almost at will. The indication for MV resides more in a decrease in respiratory compliance than in the severity of the gas exchange impairment (3).

In the past 15 yrs, ventilator-induced lung injury (4) has become one of the most important topics in respiratory critical care. A lot of attention has been paid to the fact that MV may damage the lung and eventually contribute to mortality. A major cause of ventilator-induced lung injury has been recognized in ventilation with high tidal volume, which was once commonly used to maintain lung recruitment and mean airway pressures despite relatively low positive end-expiratory

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pressure values (5). Extensive experimental work and some clinical observations led to the seminal ARDS Network trial (6), which showed a benefit in survival when patients were ventilated with 6 mL/kg instead of with 12 mL/kg (ideal body weight).

However, if we take a closer look at how MV is conducted according to the most recent indications, we discover that even when low tidal volumes are used, a very high minute ventilation is imposed to the patient. In the ARDS trial, the low tidal volume group was ventilated (day 1) with more than 13 L/min, which was not different from the control arm (6). We all know that "normal" minute ventilation is in the range of 5 L/min. What is the physiologic meaning of such high figures for minute ventilation?

Consider the Concept of Specific Hyperventilation

The lungs of a healthy adult human are comprised of open alveoli at end expiration of 2.5 L. The lungs of a patient with severe ARDS might contain just 0.5 L of gas at end expiration, and presumably a proportional amount of ventilated alveoli. In a healthy man, 2.5 L of alveoli receive 5 to 7.5 L of ventilation each minute (ratio, 2.5). In our ARDS patient, a "baby lung" (7) amounting to just 0.5 L of open alveoli receives 12.5 to 15 L per minute (ratio, 25–30), pumped under pressure by the mechanical ventilator. If this simplified model makes any sense, then each open respiratory unit of the ARDS lung receives 25- to 30-times the mechanical stress the normal lung is receiving. Why? Certainly the metabolism and therefore the CO_2 production of an ARDS patient are higher than normal, but this increase is usually below 30% (rates of elimination of CO_2 higher than 250 mL/min are exceptional observations) and therefore would justify a proportional increase in ventilation.

Why do we need such a large increase in minute ventilation? The answer is physiologically justified by an increased dead space in both the anatomical (airway) dead space and the most interesting portion, the alveolar dead space. Alveolar dead space (ventilation of underperfused or nonperfused regions of the lung) is increased substantially mainly because of two factors: microvascular occlusion and venous admixture.

Microvascular Occlusion and Alveolar Dead Space

Acute lung injury and ARDS are known as a hypoxic low-compliance diseases with a typical radiologic appearance and a consistent etiology. We know that acute lung injury/ARDS involves the vascular side and the alveolar side. Zapol et al (8) and others characterized ARDS as a pulmonary micro-occlusive, high-pulmonary-artery-pressure syndrome. When selective angiography was performed, extensive pruning of the microvascular tree was obvious (9, 10). Furthermore, in ARDS, high artery pressure is one of the major predictors of mortality (11). Underperfused or nonperfused respiratory units cannot exchange gas and, if ventilated, give rise to wasted ventilation and dead space.

Furthermore, we should consider how underperfused ventilated alveoli are obviously exposed to severe hyperventilation. It has been proven that severe hyperventilation, even during spontaneous breathing, may severely damage even normal lungs (12). Underperfused and ventilated lungs undergo severe damage and hemorrhagic edema, possibly attributable to severe local respiratory alkalosis (13). In the later phases of the syndrome, the appearance of blebs or pneumatoceles may also contribute to an increased dead space (14).

Venous Admixture and Alveolar Dead Space

Venous admixture is defined as the proportion of the cardiac output that crosses the lung parenchyma without exchanging any gas, i.e., reaching the pulmonary venous side with an oxygen content equal to the mixed venous one. We always overlook the fact that the CO_2 content also will be equal to the mixed venous one. When venous admixture is low, the effect is minor. However, in severe ARDS, when venous admixture is often close to or in excess of 30%, the effect is substantial. When the blood constituting venous admixture mixes with the blood perfusing the ideal compartment, the mixture of the two gives rise to the arterial blood. To achieve a "normal" $Paco_2$ value, with the CO_2 content of the venous admixture portion being higher, the Pco_2 of the ideal blood will have to be lower than normal. This means that the ventilation of the ideal compartment will have to be higher than normal, because the alveolar Pco_2 cannot be higher than the Pco_2 of the ideal blood perfusing it. The apparent increased difference between the arterial $Paco_2$ and mixed expired CO_2 will result in an increased wasted ventilation (increased dead space). In presence of a substantial nonperfused alveolar dead space compartment, this effect will be amplified. Because the ventilator cannot selectively direct the tidal volume, any increase in ventilation of the ideal compartment must be matched by a proportional increase in the alveolar dead space absolute ventilation.

The effect of all of these factors and mechanisms leads to a high proportion of wasted ventilation, which is involved in ventilator-induced lung injury generation. High dead space requires a high tidal volume and high minute ventilation. Dead space is strongly related to mortality (15).

As an important complement to these considerations, we learned that even the 6-mL/kg recipe is not entirely safe, because a variable but substantial proportion of patients undergo overdistention and possibly hyperventilation despite such supposedly lung-protective low tidal volume settings (16).

We have presented the evidence that MV, when applied to achieve normal blood gases in the presence of a diseased lung, is far from being devoid of major risks and may contribute to mortality and morbidity. We also provide further arguments against MV and its associated culprits, like sedation and endotracheal intubation.

Permissive Hypercapnia: Feasible, but Not the Ideal Solution

Because alveolar ventilation and arterial Pco_2 are inversely related, the obvious but unconventional solution of accepting a higher than normal $Paco_2$, enjoying the advantage of smaller tidal volumes, lower plateau pressures, and lower minute ventilation, came forward with the pioneering article by Hyckling et al (17), possibly with a previous application in patients with severe asthma (18). This approach is tempting, and it also may have direct protective effects on the lung parenchyma. However, it does not solve the problem of the unperfused regions of the lung, which will remain under severely alkalotic conditions, or the control of $Paco_2$ in patients with very high dead space. The fact that most cli-

nicians will not feel comfortable leaving untreated $Paco_2$ levels in the high range (80–90 mm Hg) is confirmed by the ARDS Network study, in which just a few patients reached $Paco_2$ levels higher than 65 mm Hg and in whom high minute ventilation was applied.

It is interesting to notice how a *post hoc* analysis of the ARDS Network low tidal volume study suggested that hypercapnic acidosis was associated with a higher survival rate in the patients ventilated with 12 mL/kg tidal volume (average airway pressure, 33 cm H_2O), but not in those ventilated with the 6 mL/kg tidal volume (average airway pressure, 25 cm H_2O) (19). The meaning of this difference in behavior is not straightforward. In summary, we can certainly say that moderate hypercapnia (60–70 mm Hg) is normally well tolerated and, in some ways, it is even claimed to be beneficial. Hypercapnia, however, is not an easy partner for a patient with low compliance, severe hypoxia, dyspnea, and high respiratory drive, and who requires a certain amount of baseline sedation to allow the ventilator to take command of the ventilatory distress. Permissive hypercapnia is a tempting concept that is simple and effective in reducing the ventilator needs. Its clinical real-life application, however, is closer to a last-ditch choice than to an everyday routine management procedure.

Extracorporeal CO_2 Removal: A Powerful Alternative to Ventilation

We suggest that extracorporeal CO_2 removal can avoid the need for MV, possibly intubation, and the concurrent levels of sedation. We propose that extracorporeal CO_2 removal, when applied by a system comparable in complexity and invasiveness to continuous renal replacement therapy, might be preferable to endotracheal intubation, MV, and sedation. It will allow full contact with the environment, normal airway physiology, and an expansion of the range of application of noninvasive ventilation.

Extracorporeal CO_2 removal will control $Paco_2$ independently of alveolar ventilation and will allow a decrease in both the spontaneous/assisted and controlled mechanical ventilatory requirements. This is exemplified in Figure 1 in patients receiving increasing rates of extracorporeal membrane oxygenation (ECMO) gas flow while undergoing pressure support ventilation. Gattinoni and Kolobow and colleagues (20–23), in experimental animals, and Marcolin et al (24), in human ARDS patients, showed how the natural lung ventilation can be decreased in proportion to the amount of CO_2 removed by the extracorporeal device.

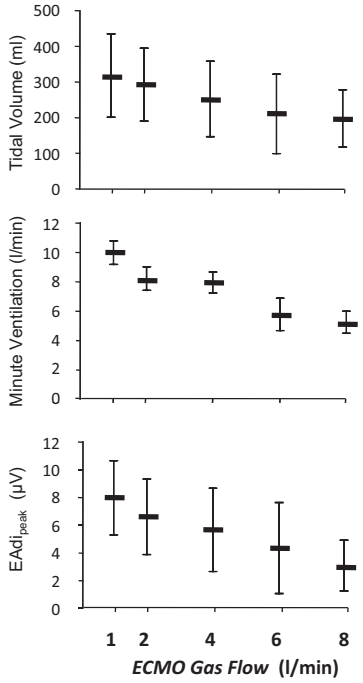

Figure 1. Effect of ventilating the membrane lung with different gas flow rates on tidal volume, minute ventilation, and peak of diaphragmatic electrical activity (*EAdi*) (registered by a multiple-array esophageal electrodes) in a patient undergoing pressure support ventilation. Each element on the graph represents the mean and SD over the course of 5 mins of stable ventilation. As extracorporeal membrane oxygenation (*ECMO*) gas flow rate is increased and more CO_2 is removed from the membrane lung, patient ventilator requirements decrease, leading to reduction in diaphragm activity, tidal volume, and minute ventilation.

Extracorporeal CO_2 removal versus ECMO

ECMO was introduced in the early 1970s as a last-ditch lifesaving procedure for patients with the most severe hypoxia. After almost 25 yrs of clinical use, with more than 30,000 patients having been treated by ECMO and reported in the international Extracorporeal Life Support Organization registry, the CESAR study was published in 2009 (25) and demonstrates the outcome advantage of ECMO when compared to MV alone. The recent H1N1 epidemic caused a comparatively high number of acutely and very hypoxic patients; ECMO was offered to many of them as a rescue procedure and some data are already available (26).

However, ECMO was and remains an invasive procedure developed to be applied in specialized centers with specific expertise. The major requirement of the procedure lies in high blood flow (3–4.5 L/min) and in the correspondingly demanding vascular access.

The physiologic requirements of oxygenation and CO_2 removal are opposite (27). Oxygen is carried in blood bound to hemoglobin, and the maximum content of oxygen is defined by the equation $CaO_2 = 0.0139 \times \text{hemoglobin} \times SaO_2 + 0.003 \times PaO_2$ (mLO_2/dL). From this equation it is immediately obvious how, under normobaric conditions, the blood oxygen content cannot exceed 15 to 20 mLO_2/dL according to hemoglobin concentration; however, the most relevant consideration refers to the fact that the extracorporeal device is fed by venous blood, whose saturation cannot be lower than a given value (65% to 70%). Therefore, in most conditions, we can only add to venous blood little more than one-quarter of its total capacity for oxygen, reaching with some difficulty a range between 7 mLO_2/dL and 5 mLO_2/dL (according to the hemoglobin concentration). This mandates extracorporeal blood flows of at least 5 L/min if we need to cope with the patient's entire oxygen consumption (250–300 mL/min) maintaining normal venous saturation levels. Blood oxygenation therefore requires a high blood flow, whereas gas flow can be, in principle, as low as the oxygen consumption.

CO_2 removal, in opposition, requires a low blood flow and a high fresh gas flow. This exactly mimics what happens in the natural lung, where hypoventilation primarily causes hypercapnia and hypoperfusion (of ventilated units) primarily causes hypoxia.

The reason for that resides in the fact that the amount of CO_2 carried in blood obeys simple physicochemical laws, with most of it in the form of bicarbonate ion. The net effect is that the normal venous blood carries at least 50 mL% of CO_2, and that this amount can be increased according to Pco_2. The peculiar condition of CO_2 transport in blood is defined by a high content at a relatively low partial pressure (40–50 mm Hg under normal conditions).

The good news is that a half liter of blood contains an amount of CO_2 equiv-

alent to the entire CO_2 produced per minute by the body metabolism. Therefore, the theory is that we can completely substitute the CO_2 elimination function of the lung by treating just 1 L of blood per minute (if our efficiency is 50%) or even a half liter (if our efficiency is 100%). Because we use, to this end, a membrane lung, high efficiency will be warranted by a high gas flow to maximize the P_{CO_2} gradient between the gas and the blood side of the membrane.

Clinical application of the CO_2 removal concept

The concept of extracorporeal CO_2 removal was developed in the Laboratory of Technical Development of the National Heart, Lung, and Blood Institute of the National Institutes of Health in Bethesda, Maryland, by Ted Kolobow and Luciano Gattinoni in 1976 to 1977 resulting in a series of publications reporting how the new approach could lead to a complete control of ventilation in sheep during awake spontaneous breathing and during controlled MV (20–23). The two authors rediscovered apneic oxygenation and low-frequency (2–5 breaths per minute) ventilation particularly designed to maintain lung volume at low positive end-expiratory pressure levels. The value of this original approach in the prevention of "barotrauma" was immediately appreciated and led to the first clinical applications.

The criteria for clinical applications, however, remained as defined in the original National Institutes of Health ECMO study in which extracorporeal gas exchange was applied as a rescue procedure in the patients with the most severe ARDS with a mortality rate higher than 90% in both the treated and control groups (28). The technique, which could benefit from a reduced extracorporeal blood flow through a venovenous bypass, exploits the residual oxygenatory function of the natural lung and merges with venovenous ECMO in cases in which venous admixture approaches 100%. Extracorporeal CO_2 removal application underscored the importance of resting the lung, avoiding further damage and ventilator-induced lung injury (29, 30).

A randomized clinical trial was performed in a small number of patients (31), but no difference in outcome could be shown between the MV and the extracorporeal CO_2 removal arm. Major problems related to the anticoagulation management might have affected the results. The technique was found useful in the treatment of severe bronchopleural air leaks to dispense with MV and allow spontaneous breathing (32).

In 1982, the concept that a low-flow, pumpless extracorporeal CO_2 removal bypass could effectively support the pulmonary function was experimentally proven (33); from then on, the arteriovenous pumpless CO_2 removal concept kept reoccurring in the experimental laboratory (34–36) and in at least one pilot human study (37). The concept of a simple, pumpless, percutaneous, arteriovenous circuit is fascinating and intriguing in its simplicity; its evolution is reached by the Novalung iLA (Talheim, Germany), initially applied as a rescue for severe hypoxia and recently applied with recognition of its essential CO_2 removal function to achieve lung-protective settings in MV (38).

As the last step in the evolution of extracorporeal CO_2 removal, in 2009 Terragni et al (39) reported on their ability to achieve tolerable hypercapnia levels despite super-protective mechanical ventilator settings (tidal volume, 4 mL/kg) in ARDS patients at risk for ventilator-induced lung injury. The investigators were able to show that, in principle, pure CO_2 removal is feasible at blood flows comparable to hemodialysis. The efficiency of the system was, however, quite limited, allowing improvements in $PaCO_2$ from 73.6 $\pm$ 11.1 mm Hg, to 50.4 $\pm$ 8.2 mm Hg and in pH from 7.20 $\pm$ 0.02 to 7.32 $\pm$ 0.03, while requiring the maintenance of controlled MV.

Foreseeable Developments and Clinical Applications

The ideal device to perform extracorporeal CO_2 removal should meet the requirements of its intended clinical application. A range of different devices probably will cover different clinical indications.

In principle, however, we should be aiming at the minimal blood flow possible, keeping in mind the physical limits imposed by the amount of CO_2 present in blood and the maximum pH compatible with a safe environment for the blood cells.

We have proposed the principle of removal of sodium bicarbonate by ultrafiltration and its substitution by a sodium hydroxide solution (40). The principle works well, but it certainly requires some refinement before reaching a possible clinical application. At a normal 25 mmol/L bicarbonate ion concentration, the system will require 2.5 L/hr of ultrafiltrate for a 10% rate of elimination of CO_2 removal and a corresponding decrease in ventilation, reaching a very high ultrafiltrate rate (and blood flows), to reach a total rate of elimination of CO_2 removal.

A different approach is achieved by loading the blood with acid to convert the bicarbonate ion to carbonic acid and, hence, to dissolved CO_2 (41). This process will increase substantially the CO_2 tension on the blood side of the membrane lung and increase the gradient for the passive transfer of CO_2 to the gas compartment. Such an approach has been shown to be feasible by use of a metabolizable acid (lactic acid). CO_2 removal at 500 mL/min blood flow increased from 100 mL/min to little more than 175 mL/min, making the device a promising tool for subsequent development.

Conclusions

For more than 40 yrs now, extracorporeal gas exchange has been utilized outside of the cardiac surgery theater only as a rescue procedure for the most severely hypoxic patients. It has been variously termed ECMO, extracorporeal CO_2 removal, interventional lung assist, and extracorporeal life support. The survival rate of such procedures, if we exclude the very high survival rates from the single report of the H1N1 epidemic in Australian and New Zealand (26), ranges between from 45% to 60%. We cannot expect a very high survival rate from a rescue procedure, particularly because this approach requires an invasive and demanding setup, with blood flows in excess of 4 L/min.

We propose a different scenario. What if instead of sedating and intubating an acutely hypoxemic patient, or what if instead of intubating an acutely hypoxemic patient in whom a noninvasive ventilation trial fails, we could apply an efficient CO_2 removal system with an invasiveness comparable to continuous renal replacement therapy and maintain spontaneous breathing, possibly with noninvasive continuous positive airway pressure, with just minimal sedation? Could we avoid ventilator-induced lung injury? We know that ventilator-associated pneumonia could be called *intubation-associated pneumonia*, because the violation of air-

way physiology operated by the tracheal tube is certainly a major determinant of the secondary infection. How significant would be the benefit of treating the patient without an endotracheal tube, or what would be the benefit of just decreasing substantially the intubation time? We know that sedation often is targeted at achieving tolerance of the tube and of the ventilator. If extracorporeal CO_2 removal is used to control the respiratory drive and dyspnea, then how significant will the clinical advantage be?

We can certainly speculate that ARDS patients could be managed without a ventilator simply by providing a high enough F_{IO_2} and airway pressure by, for example, noninvasive helmet continuous positive airway pressure. Besides that, extracorporeal CO_2 removal has been applied in patients with severe hypercapnic chronic obstructive pulmonary disease. This is an entirely new field that might even open a new field of application including the possibility of ambulatory intermittent extracorporeal removal of CO_2, given the long equilibration time of the huge, and slow, distribution volume of CO_2.

A highly efficient, low-flow CO_2 removal device, possibly combined with regional anticoagulation, therefore might be the key for a revolution in the management of acute and possibly chronic respiratory insufficiency. Moving from the indiscriminate application of MV and endotracheal intubation to a "CO_2 dialysis-like" system, given the worldwide proven safety of this kind of ambulatory device, has the potential to decrease the morbidity and mortality of respiratory failure. Blood flow as small as 300 to 500 mL/min could certainly decrease the patient's ventilator needs by more than 50%, thus relieving dyspnea and distress.

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