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## The acute respiratory distress syndrome (ARDS)

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Since the original description of the acute respiratory distress syndrome (ARDS) by Ashbaugh and colleagues, basic questions about its definition, incidence and pathophysiological characteristics are being revisited.<sup>1</sup> Indeed, improved understanding of the physiological consequences of ARDS has challenged traditional concepts of ventilatory support. The importance of this retrospection is evident by the results of a clinical trial that demonstrated a reduction in ARDS mortality simply by improving the understanding and application of basic physiological concepts. In addition to highlighting these concepts, this review will focus on two pharmacological treatments that have been the subject of several clinical trials over the past 5 years: ketoconazole and nitric oxide. The concept of ventilator-induced lung injury and resultant evaluation of lung protective strategies will also be discussed.

### Ketoconazole

Slotman et al initially reported that ketoconazole may cause a dramatic reduction in the incidence of ARDS.<sup>2</sup> In his trial, 200 mg of ketoconazole was administered daily to 71 patients at risk for developing lung injury; they reported a reduction in the development of ARDS from 31% to 6%. In a later study, Yu and Tomasa demonstrated a similar reduction in the development of ARDS in 54 patients with 400 mg of ketoconazole daily.<sup>3</sup> Both studies evaluated high-risk surgical patients. Until recently, despite these impressive results, the only other trial with ketoconazole was a non-randomized study performed in Hamilton. This study compared the incidence of ARDS in an institution that incorporated the use of ketoconazole with that in another institution that had no such strategy.<sup>4</sup> In the institution that used ketoconazole, there was a reported 30% absolute reduction in the development of ARDS.

At first glance, the rationale for even considering ketoconazole as a prophylactic agent to prevent ARDS is not readily apparent. However, ketoconazole has several potential mechanisms of action. It is an inhibitor of cyclo-oxygenase and can impair the synthesis of thromboxane. Ketoconazole also inhibits lipo-oxygenase and reduces the production of LTB<sub>4</sub> – a neutrophil chemo-attractant. As such, ketoconazole may prevent the development of neutrophil-mediated lung injury. Given its potential anti-inflammatory properties, low cost, and ready availability, early reports of the benefit of ketoconazole in preventing ARDS stimulated a great deal of excitement.

Despite the initial promising reports, it was only recently that the NIH/ARDS network published the findings of a prospective, randomized, controlled trial of ketoconazole.<sup>5</sup> The study had a 2x2 factorial design: 117 patients were randomized to receive ketoconazole and 117 to placebo, in addition to being randomized to conventional vs. a low lung volume ventilation strategy. As ketoconazole requires a low pH for absorption, drug delivery was assured via acidification of the gut (using Coke Classic™ to dissolve the medication). However, despite improved absorption of drug (serum levels were on average 10 times higher than in the study by Yu and Tomasa), the ARDS/Net trial did not demonstrate a significant improvement in outcome (Figure 1).



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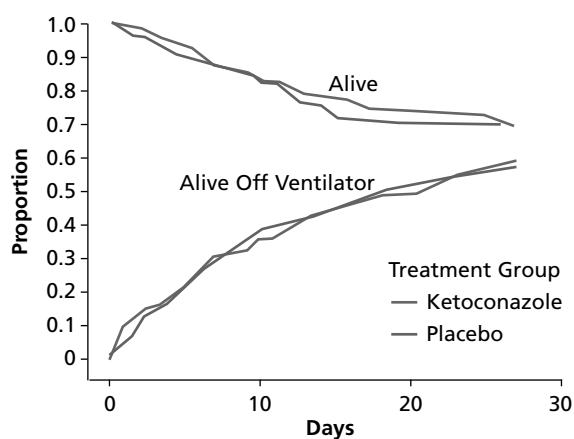
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**Figure 1: There was no difference in the proportion of patients who were “alive” or “alive off the mechanical ventilator” in the ketoconazole and placebo groups.<sup>5</sup>**



Secondary biological outcomes even cast doubt on the role of ketoconazole as an anti-inflammatory agent. Plasma IL-6 and urinary metabolites of thromboxane were not affected by ketoconazole administration. The major criticism was that the study involved patients with *established* ARDS. Consequently, it was felt to differ from the earlier studies that evaluated ketoconazole as a prophylactic agent to *prevent* ARDS. However, as pointed out by the ARDS/Network authors, the study by Yu and Tomasa did include “several” patients with established ALI or ARDS. Another potential difference was the earlier studies focused on surgical patients, whilst the ARDS/Network trial included both medical and surgical patients. In a subgroup analysis, however, they could not find a benefit even in the surgical subgroup. Despite the disappointing results of the ARDS/Net trial, some interest remains in evaluating ketoconazole as a prophylactic agent in high risk patients.

### Nitric oxide

The use of nitric oxide (NO) to treat ARDS started after NO was identified as the endothelial relaxant factor. Rossaint et al described a reduction in venous admixture with inhalation of NO in 9 patients with ARDS.<sup>6</sup> This led to the hope that NO would not only improve oxygenation, but also allow for less intense mechanical ventilation and a reduction in FiO<sub>2</sub>, both effects potentially leading to a reduction in ventilator-induced lung injury. Despite the initial promise, subsequent studies have identified several limitations of administering NO in patients with ARDS. First, the duration of response seems to be short-lived. Second, not all patients have experienced an improvement in oxygenation or a reduction in pulmonary arterial pressures with inhaled NO (iNO).

### Trials of NO therapy in adults

Both of these limitations were illustrated in one of the larger studies of NO in ARDS by Dellinger et al.<sup>7</sup> 177 patients with ARDS were randomized to placebo or one of 5 doses of iNO. Although there was an initial improvement in venous admixture in the iNO group, no benefits with NO were observed after 72 hours compared to placebo. In addition, there was no benefit in overall survival or in the duration of mechanical ventilation. However, in the group that received 5 ppm of NO, there was a statistically significant reduction in duration of mechanical ventilation. It is not known if this represents a dose effect or an effect of multiple comparisons of the data. Importantly, only 60% of patients in the iNO arm actually responded to iNO inhalation (defined as a >20% increase in PaO<sub>2</sub>). Furthermore, a surprising 25% of patients also had a positive “response” to placebo. This observation reinforced the notion that oxygenation has significant variability in this group of patients and that a large number do not experience any acute benefit of NO administration. Indeed, identification of patients who will respond to NO administration has been problematic.

One criticism of the NO trials has been that the evaluation of NO should be restricted to patients who demonstrate an initial response to NO and not all comers. To this end, a recent multi-centre European study attempted to overcome some of the concerns that perhaps only a subgroup of responders benefit from iNO.<sup>8</sup> They enrolled only patients who had ARDS and who responded acutely to iNO. 180 patients were randomized to placebo or iNO. There was no difference in mortality (40% in controls and 44% for iNO), nor did iNO significantly reverse acute lung injury. However, the iNO group did develop “severe” ARDS less frequently (10% vs 2.2% for placebo and NO, respectively).

It is uncertain how a drug that has such a temporary and relatively small effect on oxygenation can lead to an overall survival benefit in patients with ARDS. However, the capacity to acutely respond to NO may be important. In a study from Montreal, Michael et al demonstrated that the ability to reduce FiO<sub>2</sub> at 72 hours correlated with survival (70% vs 30% in patients whose FiO<sub>2</sub> could not be reduced).<sup>9</sup>

At present, NO seems to have a role in patients with refractory hypoxemia and who are *in extremis*. In our experience, some patients with severe refractory hypoxemia have had dramatic improvements in oxygenation. Consequently, our view is that the use of NO is analogous to the use of thrombolysis for massive PE. Namely, that it be reserved for patients with who are failing from hypoxemia or right ventricular failure despite conventional methods of support. However, given the relative rarity of refractory hypoxemia, the claim of benefit for NO in this setting is difficult to substantiate.

## Trials with NO in newborns

In contrast to the experience with NO in adults, the evidence for its beneficial effects in treating newborn respiratory distress has been more persuasive. In both persistent pulmonary hypertension of the newborn (PPHN) and respiratory failure of newborns, NO has been shown to reduce the need for extracorporeal membrane oxygenation (ECMO).

In a study by Roberts et al, 58 infants with PPHN were randomized to receive either NO or placebo in a blinded fashion.<sup>10</sup> There was a reduction in oxygenation index ( $\text{FiO}_2 \times \text{mean airway pressure} / \text{PAO}_2$ ); 16 of 30 infants (53%) in the control arm experienced an improvement in oxygenation, whereas there was an increase in oxygenation in only 2 of 28 infants (7%) in the control group. Importantly, there was a reduction in the need for ECMO therapy: ECMO was required in 71% of the control group and 40% of the NO group ( $P = 0.02$ ).

Similarly, in the Neonatal Inhaled Nitric Oxide Study Group (NINOS) trial, fewer patients in the NO group received ECMO (39% vs. 54%,  $P = 0.014$ ).<sup>11</sup> The NO group had significantly greater improvement in  $\text{PaO}_2$  (mean  $\pm$  SD increase,  $58.2 \pm 85.2$  mm Hg, vs.  $9.7 \pm 51.7$  mm Hg in the controls;  $P < 0.001$ ) and in the oxygenation index (a decrease of  $14.1 \pm 21.1$ , vs. an increase of  $0.8 \pm 21.1$  in the controls;  $P < 0.001$ ).

A recently published study by Clark et al confirmed these observations in 248 neonates with an oxygenation index (OI) greater than 25. Unlike the NINOS trial, this study used a lower dose of NO (20 ppm) over a shorter period of time (maximum 96 hours). The evidence revealed that NO reduced the need for oxygen therapy at 30 days (an indicator of chronic lung disease) from 20% to 7%.<sup>12</sup>

Despite these results and the seeming importance of reducing the need for ECMO therapy (from both a cost and patient perspective), there was no survival advantage. Interestingly – similar to the situation in adults – the neonatal studies demonstrated that not all infants respond to NO. In the NINOS trial, 66% of the infants in the NO group had a partial or full response to the initial administration of NO. The majority of the infants who did not have complete responses at 20 ppm of NO had no response to the study gas at a higher concentration of NO (77% in the NO group vs. 81% in the control group). Identification of responders vs. nonresponders has been problematic. An interesting observation in both adult and pediatric patients is that phosphodiesterase (PDE) inhibition seems to provide additional benefit to patients who only partially respond to iNO. Sildenafil and zaprinast (both inhibitors of PDE<sub>5</sub> which is found in the lung) have been shown to increase the response to iNO. Sildenafil and persantine (a non-specific PDE inhibitor) have also been shown to reduce the rebound pulmonary arterial hypertension and subse-

quent hemodynamic collapse that becomes problematic in some patients after discontinuation of NO.

### *The future of NO therapy in adults*

The future of NO in adult respiratory failure will likely be in applications that exploit its anti-inflammatory properties.

- NO has effects on neutrophils and platelets making it attractive as an agent to reduce lung injury. There is evidence that NO reduces the incidence and severity of reperfusion injury in animal models of lung ischemia and transplantation. We are currently evaluating the results of a study on the use of NO to prevent ischemia-reperfusion injury in patients undergoing lung transplantation.

- NO may also have a role in preventing ischemia-reperfusion injury in distal non-pulmonary organs. Kubes et al has challenged the notion that the effects of NO are localized.<sup>13</sup> He demonstrated that NO is capable of reducing neutrophil retention and neutrophil-mediated injury in animal models of gut ischemia. If this observation is correct, then iNO may be useful in patients with gut ischemia or limb ischemia-reperfusion injury.

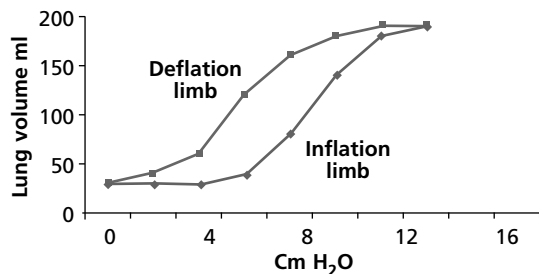
- Researchers in London, Ontario, have provided evidence for a therapeutic role of NO as an anti-microbial agent.<sup>14</sup> Earlier studies demonstrated the antimicrobial effects of NO *in vitro*, but in this recent trial using a rat model of *Pseudomonas aeruginosa* pneumonia, inhaled NO significantly reduced bacterial load, pulmonary myeloperoxidase activity, and the observed pneumonia-induced rise in calcium-independent NO synthase activity. However, there was no effect on gas exchange or hemodynamics.

### *Soluble NO donors*

Despite the favorable biological and anti-inflammatory properties of NO, the clinical benefits have not yet been determined and there are practical limitations that may preclude its use. First, specialized equipment is required to ensure accurate delivery, and second, the commercial costs of NO may make it cost-prohibitive.

The use of novel NO donors has been explored with interest. These soluble NO donors are formed when NO reacts with nucleophiles to produce NONOates. NONOates are less cumbersome to deliver because they non-enzymatically release NO once aerosolized and have similar hemodynamic effects as inhaled NO. There are a variety of NONOates available, each with variable half-lives that allow them to be nebulized at periodic intervals. Indeed, recent work from researchers at the Children's Hospital in Cincinnati demonstrates that NONOates, when aerosolized in pigs with oleic acid-induced lung injury, selectively reduced pulmonary vascular resistance and improved venous admixture.<sup>15</sup> The magnitude of the effect appears to be similar to that of inhaled NO. Whether or not NONOates share similar anti-inflammatory properties as inhaled NO needs to be evaluated. In

**Figure 2: Pressure volume curve of the lung demonstrating the upper and lower inflection point. Note that during the deflation limb that the compliance of the lung is improved.**



addition, the systemic and regional effects of these agents, when administered over prolonged periods, needs to be evaluated.

### Lung protection strategies

#### *Ventilator-induced lung injury*

Two concepts have culminated in a clinical trial that shows that the manner in which ARDS patients are ventilated can have a significant impact on mortality. The first concept is the notion that ARDS is not a homogeneous process characterized by “stiff” lungs. Rather, it is now known to be an inhomogeneous process characterized by a reduction in the number of functional alveolar units. This observation is tied directly into the second concept of ventilator-induced lung injury (VILI). It was suggested that the use of conventional tidal volumes was likely inappropriate for patients with ARDS and that it actually perpetuated or even caused lung injury via overdistention of alveolar units. Enthusiasm for “lung protection strategies” flourished after the cohort study by Hickling who demonstrated a reduction in mortality compared to that predicted through the use of a restriction of lung volume.

The principals of limiting ventilator-induced lung injury are illustrated by examination of the pressure volume curve of the lung (Figure 2). Initially, during lung inflation, there is little increase in lung volume with increase in airway pressure. At some point, however, lung compliance improves owing to recruitment of alveoli. This point has been termed the “lower inflection point.” As the lung expands, the limit of alveolar distention is reached and the compliance curve begins to downturn. At this point, there is felt to be alveolar overdistention. This is termed the “upper inflection point.” It has been conclusively demonstrated that ventilation at lung volumes either below or above the lower and upper inflection points leads to both epithelial and endothelial injury.

The injury at high lung volumes is felt to be secondary to mechanical stretch as opposed to pressure *per se*. In contrast, during ventilation at lung volumes below the lower inflection point, the injury may be the result of shear stress injury that occurs with repetitive opening and closing of lung volumes. The pressure volume curve also demonstrates another feature, namely that as the lung is inflated and alveoli recruited, the deflation limb of the lung shifts to the left. Consequently, for a given pressure, the lung volume is greater. This has led investigators to start evaluating the importance of lung volume recruitment to maintain patients on the deflation limb of their pressure volume curve. However, to date, most clinical studies have focused on limiting lung volumes. Only one trial has evaluated a strategy to ensure that the lung is maintained above the lower inflection point.<sup>16</sup>

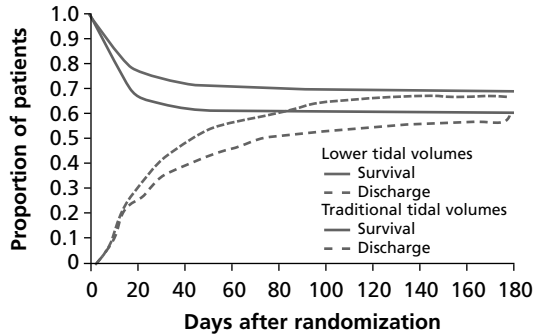
Despite the perceived importance of VILI, it was initially unclear how the adoption of lung protection principles to reduce VILI could lead to a reduction in mortality. Most patients with ARDS die from multi-organ dysfunction and not refractory hypoxemia. Consequently, strategies that reduce the severity of hypoxemia would not be expected to have a significant impact. However, recent work suggests that VILI is also capable of releasing inflammatory mediators into the systemic circulation. Tremblay et al, in an *ex vivo* model of lung injury, demonstrated that the use of high tidal volumes or low levels of PEEP led to high lung lavage levels of inflammatory cytokines.<sup>17</sup> Indeed, these initial observations have been reproduced in patients with ARDS.

In a prospective randomized trial, Ranieri et al randomized patients with ARDS to receive conventional ventilation strategy (to keep PaCO<sub>2</sub> between 35-40 mm Hg) or a lung protection strategy using a tidal volume and PEEP level based on individual pressure volume curves.<sup>18</sup> Patients in the conventional group had an increase in both systemic and lung lavage concentrations of inflammatory cytokines. After 36 hours of randomization, the inflammatory mediators were significantly lower in the lung-protection group. Based on these observations, an inappropriate ventilator strategy may lead not only to regional injury, but also to perpetuation of MSOF. In this regard, efforts to prevent VILI may lead to a reduction in MSOF and thus death.

#### *Clinical trials of lung protective strategies to prevent VILI*

Initial randomized clinical trials evaluating the effect of lower tidal volumes on outcome were disappointing. There was even a suggestion that lung volume restriction was harmful as it was associated with a greater use of neuromuscular

**Figure 3: Results of the ARDS/Net low lung volume trial. Use of a low lung volume in patients with ARDS led to a 25% reduction in mortality. Although there was an improvement in ventilator-free days, the effects were solely due to the reduction in mortality.<sup>8</sup>**



blockers, a greater need for dialysis (perhaps related to the lower pH from a higher PaCO<sub>2</sub>), and a trend to towards higher mortality.

In a study by Stewart et al, mortality in the lung volume restriction arm was 50% compared to the control arm (47%), while in a study by Brochard et al, mortality was 47% and 39%, respectively.<sup>19,20</sup> However, a recent NIH-sponsored study has vindicated much of the earlier animal studies and clinical trials.<sup>21</sup> In this trial, patients were randomized to receive either “conventional” tidal volumes (12 ml/kg; tidal volume was reduced if plateau pressure was greater than 50 cm H<sub>2</sub>O) or a lower tidal volume (6 ml/kg, and maintain a plateau pressure between 25 and 30 cm H<sub>2</sub>O). The trial was stopped early after an interim analysis demonstrated a survival benefit in the low lung volume group (Figure 3). There was a 25% reduction in mortality from 40% in the conventional arm to 31% in the low lung volume arm (confidence interval, 2.4 to 15.3% difference between the groups). The benefit of a lung protection strategy seemed to be independent of the severity of the lung compliance at baseline. In addition to a mortality effect, the number of days alive and free of mechanical ventilation was lower in the intervention arm. However, this effect was solely due to the reduction in mortality as the median duration of mechanical ventilation was 8 days for survivors in both groups. Interestingly, the number of days with non-pulmonary organ failure was lower in the intervention arm and the plasma interleukin-6 concentration was decreased compared to the control group. This again supported the notion that a lung protection strategy achieved its benefit through a reduction in the systemic release of inflammatory mediators and reduction in severity

of MSOF. Unlike previous studies however there was no difference in the use of neuromuscular blockers.

It is difficult to reconcile the differences in the results of the ARDS/Net study with earlier clinical trials evaluating a lung volume restriction strategy because the ARDS/Net study differed in several ways making direct comparisons difficult.

- First, the method of determining ideal body weight (and hence tidal volume) was different from earlier trials.

- Second, patients in the low tidal volume arm had higher respiratory rates that may have led to significant auto-PEEP – in turn leading to improved alveolar patency or recruitment.

- Third, the respiratory acidosis was corrected with bicarbonate. This may have reduced the number of patients dialyzed and could have reduced some of the as yet to be determined adverse effects of hypercapnic acidosis.

The major criticism of this study, however, is that it was stopped early by the Data Safety Monitoring Committee after a mortality benefit in the treatment arm was discovered. Indeed, frequent interim analysis of trials and early stopping is often problematic as it may introduce bias and lead to an overestimation of treatment effect. Consequently, the 25% reduction in mortality may be exaggerated.

In addition to lung over-distention, VILI also incorporates the concept that under-distention of alveolar units can also lead to injury. To date no study has evaluated the relative benefit of a strategy that attempts to recruit and maintain alveolar patency. The study by Amato et al examined the effect of a multifaceted strategy that minimized lung volume; recruited alveoli through a sustained inflation; used a level of PEEP above the closing pressure of the lung; and utilized a pressure volume curve to define the optimum lung volume and PEEP.<sup>16</sup> Using this strategy, they demonstrated an impressive reduction in mortality. The major criticism of this study, however, is that the control group was significantly disadvantaged by a protocol that allowed for significant over-ventilation and that the observed results were not due to a benefit in the treatment arm, rather a detrimental outcome in the control group.

In order to make specific recommendations about the optimum strategy, the relative effects of lung volume reduction, alveolar recruitment, and level of PEEP need to be determined. To this end, a multi-centre Canadian study spearheaded by Maureen Meade, and a separate study by the ARDS/Net group, are evaluating the effect of lung volume recruitment and high PEEP on outcome in ARDS. In the Canadian trial, over 800 patients will be randomized to either low tidal volumes (iden-

tical to the ARDS/Net trial) or a low tidal volume with a lung open approach. The lung open approach will utilize both periodic sustained inflations at 40 cm H<sub>2</sub>O CPAP for 40 seconds and high levels of PEEP (up to 20 cm H<sub>2</sub>). This strategy will hopefully ensure both alveolar recruitment and maintenance of alveolar patency.

## Summary

ARDS continues to be a common component of multisystem organ dysfunction and primary lung injury. Unfortunately, no pharmacological intervention has proven to be efficacious in reducing mortality in patients with ARDS. An improved understanding of ARDS and the notion that prior ventilator strategies may have been injurious has led to a reflection of how patients are supported. The low lung volume ARDS/Net trial demonstrated a reduction in mortality with the implementation of a "lung protective" strategy, however, it is a matter of perspective if it was the intervention that produced the benefit, or if we finally got it right and stopped causing harm.

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