Rescue Strategies in Severe Refractory Hypoxemic Respiratory Failure: Taking a Step Back

Comparative effectiveness research is an initiative of the Affordable Care Act. The Patient-Centered Outcomes Research Institute has been established to provide comparative effectiveness information to assist patients, clinicians, purchasers, and policy makers in making informed health decisions. This concept applies to rescue strategies in patients with ARDS, a common and severe form of acute lung injury requiring life support with mechanical ventilation. The goals of mechanical ventilation are to sustain life by restoring adequate gas exchange, to avoid ventilator-induced lung and diaphragmatic injury, and to prevent oxygen toxicity. These goals are accomplished in most patients with the ARDS Network lung-protective ventilation strategy: a tidal volume of 4–8 mL/kg of ideal body weight, a plateau pressure of ≤30 cm H_2O, and optimal lung recruitment with application of PEEP.[1]

Mortality from ARDS in most patients is mainly due to sepsis and multiple organ failure. However, 16% of deaths in severe ARDS are attributable to refractory oxygenation failure.[2] Published studies have used various definitions to categorize severe refractory oxygenation failure: P_{aO_2}/F_{IO_2} of <100 mm Hg; Murray lung injury score of >3, or oxygenation index of >30 despite application of lung-protective strategies.[3] In the absence of high quality evidence-based protocols and algorithms, physicians have employed a number of rescue strategies, such as prone positioning, inhaled nitric oxide or prostacyclin, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation (ECMO) to correct hypoxemia until lungs recover with the hope of improving survival in patients with reversible lung diseases. It is recommended that clinicians initiate the rescue strategy within 96 h of the onset of ARDS, when there is potential for alveolar recruitment. The choice of rescue strategy is primarily dependent on availability of equipment, provider expertise, preference, and patient selection. High-value treatment considerations should balance efficacy, safety, and cost of rescue strategies. Published clinical trials have reported that rescue strategies improve oxygenation, but none have documented survival benefits in heterogeneous groups of subjects.[3] This raises many difficult medical and ethical therapeutic dilemmas regarding rescue strategies. Physicians struggle to answer many questions: whether to initiate rescue strategies after carefully considering benefit and harm; once implemented, how long to continue rescue strategies if the desired outcome is not achieved; and whether to refer patients to centers of excellence.

SEE THE ORIGINAL STUDY ON PAGE 127

In this issue of RESPIRATORY CARE, Franco et al[4] report their experience in treating patients with severe oxygenation failure over a period of 6 y from 2005 to 2010. This is a single-institution retrospective comparative effectiveness study from the Mayo Clinic, a tertiary care referral center. The study is designed to examine the trend and effectiveness of 4 major rescue strategies both collectively and individually in subjects with severe oxygenation failure, refractory to lung-protective conventional mechanical ventilation, and PEEP optimization. In 793 of a total of 1,032 subjects, the cause was ARDS, but in a small but significant minority, the cause of severe hypoxemia was not known. However, these subjects were included in the final analysis. Many subjects had underlying chronic comorbidities of unknown severity: preexisting lung diseases, such as COPD, interstitial lung diseases, and pulmonary arterial hypertension; diabetes mellitus; liver cirrhosis; or underlying immunosuppressive state, including organ transplant recipients. Although subjects from trauma/surgical ICU were included, none had trauma as a cause of ARDS. Of 239 subjects (23%) in the rescue strategy arm, 59 received a combination of rescue strategies, and 180 received individual therapies.

Inhaled vasodilators were the most common modality of rescue strategy given in 189 subjects either alone or in combination. Pulmonary hypertension was present in 96 subjects (40%) in the rescue strategy group. Preference of a specific rescue strategy was determined by the practice pattern of various ICU intensivists. The propensity scoring model was used to evaluate the association of each rescue strategy with hospital mortality. The authors concluded

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that subjects who received rescue strategies as a group had worse outcome measures (ie, in-hospital mortality, ventilator-free days, and ICU stay). The strength of the study is inclusion of a large number of subjects. The authors used a rigorous screening process to select subjects with severe hypoxemia as defined by Murray lung injury score of >3. The comparative effectiveness study is unique in that it assessed the effectiveness of 4 main rescue strategies individually and were compared with conventional ventilation therapy. There are many limitations, including a retrospective observational study design; subjects who received rescue strategies were younger and sicker with respect to hemodynamic and respiratory impairments. The rescue strategy group included more subjects with sepsis and shock. This raises the question of whether institution of rescue strategies is a risk marker or a risk factor for worse outcome. The fact that some subjects had other causes of severe hypoxemia makes comparison difficult with other studies of subjects with ARDS. Nevertheless, the findings of poor outcomes with rescue strategies are in agreement with other studies with a few exceptions. The impact of rescue therapies has been extensively investigated over the decades. Studies have reported disparate findings. Many authoritative review articles have succinctly summarized these findings.[5]

Inhaled NO and aerosolized prostacyclin improves ventilation/perfusion matching by increasing circulation to better-ventilated alveoli and reducing pulmonary hypertension associated with ARDS. Adhikari et al[6] examined the effect of inhaled nitric oxide on in-hospital mortality in subjects with severe ARDS ($P_{aO_2}/F_{IO_2} \leq 100$ mm Hg). The meta-analysis included data from 9 trials with 1,142 subjects.[6] They concluded that inhaled NO does not reduce mortality. Another meta-analysis of 25 studies showed that inhaled prostacyclin improved oxygenation and decreased pulmonary artery pressures but may be associated with harm by producing hypotension.[7]

ECMO is a technique that dissociates mechanical ventilation and gas exchange, thereby reducing ventilator-associated lung injury. Multiple studies have evaluated the effect of ECMO on mortality in subjects with severe acute respiratory failure. The CESAR study[8] was a United Kingdom-based multi-center randomized trial. Subjects who required ECMO were treated in a specialized referral center. ECMO improved 6-month survival without disability and was cost-effective.[8] However, a French observational study found no difference in mortality in subjects with severe influenza A (H1N1)-related ARDS treated with ECMO. A subgroup analysis showed improved survival in severely hypoxemic and younger ECMO-treated subjects.[9] A retrospective, case-control study showed that subjects with ARDS who received ECMO treatment had higher in-hospital and 6-month survival rates.[10] As per the Extracorporeal Lung Support Organization guidelines, ECMO is indicated in patients with severe hypoxemic respiratory failure with a P_{aO_2}/F_{IO_2} of <100 mm Hg despite optimization of the ventilator settings, including the tidal volume, PEEP, and inspiratory-expiratory ratio, or hypercapnic respiratory failure with an arterial pH <7.20. It should be considered if P_{aO_2}/F_{IO_2} is <150.[11]

The PROSEVA study,[12] a multi-center, prospective randomized controlled trial, showed that prone-positioning sessions of at least 16 h decreased 28- and 90-d mortality. A meta-analysis of 7 randomized trials showed that ventilation with prone positioning improved oxygenation and survival but increased the risk of complications: accidental dislodgement and obstruction of endotracheal tubes.[13] The authors recommended that it should be considered in severe oxygenation failure. Subsequent meta-analyses have confirmed these findings and additionally suggested that the improved survival from prone positioning is only observed when combined with low tidal volume and high levels of PEEP ventilation.[14] The OSCAR trial,[15] a multi-center randomized study, documented that the use of high-frequency oscillatory ventilation had no significant effect on 30-d mortality in subjects undergoing mechanical ventilation for ARDS.

In summary, in the absence of unequivocal high-quality evidence to support the effectiveness of rescue strategies, the decision to institute rescue strategies is a complex process and is made on a case-by-case basis. The patient-provider shared decision should be guided by patient-centered goals of care based on prognosis for long-term survival without disability, benefits and burdens of rescue strategies, and patient preference. The patient should be offered the benefit of a time-limited therapeutic trial with a provision to discontinue therapy if the goals of care are not achieved.

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