

When isn't the cause of acute respiratory distress syndrome important?

Andrew D Bersten

Acute respiratory distress syndrome (ARDS) is a fundamental intensive care disease. Although the commonly used definitions of the 1994 American–European Consensus Conference¹ do not require that ventilatory support be used, most clinicians and some other definitions assume that the patient is intubated and ventilated. Major recent contributions in this area have centred around reducing mortality from multiple organ dysfunction with lower tidal volume ventilation,² and reducing ICU morbidity with a parsimonious approach to fluid therapy.³ These advances have widespread implications. In Australia, the incidence of acute lung injury is higher than recognised by most clinicians:⁴ one in nine non-cardiothoracic ICU patients develops acute lung injury; as acute lung injury develops in a third of those “at-risk”, it appears that one in three ICU patients is “at-risk”.

In parallel, there is a growing body of research into the long-term morbidity suffered by ARDS survivors. In addition to long-term abnormalities of pulmonary function, morbidity may include reduced quality of life and impaired neurocognitive function. For example, Herridge and colleagues⁵ reported an extensive follow-up of 109 ARDS survivors. Lung volume and spirometric measurements were normal by 6-month follow-up, but the diffusing capacity for carbon monoxide was 72% of predicted at 12 months. Only half the patients had returned to work by 1 year. Their scores on the SF-36 General Health Survey were below those of age- and sex-matched control populations for all domains apart from emotional role, and scores for physical role were severely reduced. Subjectively, muscle weakness and fatigue were the main reasons for reduced function. The absence of both systemic corticosteroid therapy and ICU-acquired illness, as well as rapid resolution of both lung injury and multiple organ dysfunction, correlated with better functional status.

Prolonged neurocognitive sequelae are also common in ARDS survivors, with half falling below the 6th percentile of the normal distribution for cognitive function.⁶ Mechanisms behind this disturbing finding are uncertain, but there is evidence of unexpected cerebral atrophy,⁷ and a correlation with the degree of hypoxaemia.^{6,8} Impaired glucose control, hypotension, sedatives, and inflammatory mediators may also play a role. Clearly, these data demand that we start to consider quality of life and neurocognitive function as important treatment outcomes.

In this issue of the Journal (*page 302*), Li and colleagues⁹ report their experience with long-term outcomes of ARDS following severe acute respiratory syndrome (SARS). Of 69 patients with acute respiratory failure and SARS admitted to their ICU, 59 developed ARDS. Twenty-seven of these were intubated, with 14 survivors (52%). Of the 32 ARDS patients who did not require intubation, 31 (97%) survived. Consistent with previous research, the patients who required ventilation had a persisting reduction in diffusing capacity at 12-month follow-up. On the SF-36 Health Survey, health-related quality of life was near normal by 6-month follow-up in patients aged up to 40 years, but remained impaired at 12 months in older patients.

Compared with Herridge et al's ARDS patients,⁵ patients with ARDS caused by SARS appear to have a better outcome, but differences in definitions of ARDS introduce an important confounding factor. Herridge et al enrolled a group of patients with particularly severe disease, with an initial $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg while intubated and receiving 5 cmH₂O positive end-expiratory pressure, and airspace opacity on all four quadrants of the chest radiograph. Consequently, their cohort was sicker than the cohort studied by Li et al:⁹ they had higher APACHE II scores (median, 23 versus 10), higher initial multiple organ dysfunction scores (median, 9 versus 3) and longer ICU stay (median, 25 days versus 9 days). Li and colleagues⁹ also raise the possibility of age-related impairment of quality of life, with patients older than 40 years having greater impairment. However, as their analysis involved a group of 10 patients, which was then subdivided by age, these results require careful interpretation.

All Li et al's patients received steroid therapy (average, 178 mg/day),⁹ and it is surprising that the association between steroids and neuromuscular complications described by Herridge et al⁵ and the ARDS Network¹⁰ was not apparent. Perhaps this was due to a combination of less severe illness and short duration and low dose of steroid therapy in the SARS patients. Alternatively, as SARS tends to result in single-organ failure, while ARDS with other pulmonary and non-pulmonary causes tends to be a multisystem disease, SARS may have less severe systemic sequelae.

The SARS coronavirus has recently been shown to bind angiotensin-converting enzyme 2 (ACE2) in the lung, reducing negative regulation and increasing local production of angiotensin II, leading in turn to acute lung injury.¹¹ In

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addition, inhibition of ACE, or augmentation of ACE2, protects mice from lung injury in a variety of common ARDS models.¹² This suggests a novel therapeutic pathway that targets an early critical phase in the development of ARDS. These exciting mechanistic data also suggest why SARS may lead to predominantly single-organ (lung) failure. Perhaps this mechanistic difference will allow us to understand which aspects of treatment and outcome in ARDS are lung-specific, and which are attributable to multiple organ dysfunction. The report by Li and colleagues is an early step on this important path.

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