ARDS: Predicting Mortality and Improving Survival

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Acute respiratory distress syndrome (ARDS) is a devastating clinical disorder that affects critically ill patients with a wide variety of underlying diseases. Intense research over the last 20 years has conclusively established that ARDS is an inflammatory disorder with broncho-alveolar lavage (BAL) studies confirming the presence of increased numbers of acute inflammatory cells (neutrophils and macrophages) and pro-inflammatory cytokines.

The article by Vigg et al in this issue of JAPI is a welcome addition to the epidemiology of ARDS from this country. Although their data is retrospectively collected, their careful definition and documentation of the patient population, APACHE and MODS scores, modes of ventilation and causes of death should be a routine part of data collection in every ICU in the country. Many opportunities to expand on their theme have been missed however. It would have been ideal to have compared the group of 98 patients who died of ARDS with those that survived to try and determine the clinical risk factors predictive of a poor outcome. Several prospective studies using the NAECC (North American-European Consensus Conference) definition of ARDS have identified risk factors that are independent predictors of mortality. Data of this kind gives the practicing intensivist practical information that gets beyond the cytokines and mediators that characterise so much of ARDS research these days. A recent Indian study by Gupta from PGI, Chandigarh showed how mortality data can be more usefully analysed. Attempting to correlate survival with age, etiology, disease severity scores and organ failure using multivariate analysis, he found that sepsis, APACHE II score > 57 and SAPS II SCORE > 39 were all associated with increased risk of mortality. Another study by Doyle et al showed that liver dysfunction, sepsis and non-pulmonary organ system dysfunction during the period between hospitalisation and admission to the ICU were significantly associated with increased mortality. A French study by Monchi et al of 259 patients with ARDS in a medical ICU found that cirrhosis, sepsis and the occurrence of right ventricular dysfunction were independent predictors of death. An American study showed that in addition to sepsis and cirrhosis, organ transplantation, HIV, active cancer and age above 65 years were all independent predictors of mortality. A recent large prospective clinical study by Nuckton found that a raised pulmonary dead-space fraction was independently associated with mortality. Interestingly in most of these studies neither the initial oxygenation abnormality (PaO2/FiO2 ratio) nor the ALI (acute lung injury) score predicted mortality. Vigg et al have missed an opportunity to increase the scientific value of their mortality data by not analyzing further their patients dying of ARDS to determine similar predictors of mortality.

Are there any biological markers that can identify which patients with ARDS are more likely to die? Raised levels of procollagen III peptide in early BAL samples and persisting BAL neutrophilia also predict a prolonged clinical course with progression to pulmonary fibrosis in patients with ARDS. Ware et al showed that higher plasma levels of von Willebrand factor antigen in ARDS patients independently predicted mortality early in the clinical course. The great strides in genomics are also having a direct impact in the ICU. An intriguing article by Marshall provided the first evidence of a genetic influence in ARDS. Ninety six patients with ARDS were genotyped for angiotensin converting enzyme (ACE) polymorphism. They found that the frequency of the DD genotype for ACE was not only associated with development of ARDS but also adversely affected survival. They went on to postulate that administration of ACE-inhibitors might lower the risk of development of ARDS in high-risk patients and improve its outcome. Intensivists are in need of diagnostic tools like these to identify populations at risk so resources can be better utilized.

The mortality of ARDS remains high but there is optimism on the horizon with the publication of the ARDS Net study in 861 patients which showed that ventilation with lower tidal volumes (6 ml/kg predicted body weight) resulted in a 21% reduction in mortality compared to a control group ventilated at conventional volumes (12 ml/kg). Although there has been criticism of the design of this study there is now little doubt that these lung protective strategies are the standard that should be followed when it comes to ventilating all patients with ARDS. It is now clear that the high volume, high pressure ventilatory strategies used in the past caused and propagated worsening ARDS by adding to the alveolar inflammation referred to at the start of this editorial. A landmark study by Ranieri et al went one step beyond and showed that high tidal volume ventilation not only increased alveolar inflammation, but also disseminated inflammatory cytokines which explains why our earlier ventilatory strategies in ARDS were flawed. In fact the ARDS Net trial was the first randomised clinical trial which showed an intervention actually resulted in significantly improved survival in ARDS.
lifting the therapeutic nihilism and gloom from the critical care community. In the words of Baudouin “the Holy Grail of clinical ARDS research had finally been reached”.12

What is of equal interest is another interesting paradox in clinical lung injury research. Despite earlier ARDS studies almost uniformly showing no intervention tried carried a survival benefit, groups from the UK and America produced persuasive evidence of a declining mortality from ARDS from their ICU’s well before the seminal findings of the protective ventilatory strategy propagated by the ARDS Net study. Abel from his ICU in the UK13 reported a decline in mortality of his ARDS patients from 66% in the early 1990’s to 34% in the late-90’s. A US group14 reported an equally sharp decline in mortality over this decade from 60% to 36%. It is interesting to note that these reduced mortality rates were similar to those reported in the intervention limb of the recent ARDS Net study. One possible explanation of this paradox is that a general improvement in the practice of intensive care medicine was responsible. Another possible explanation for the fall in mortality may also have been due to the adoption of beneficial ventilatory strategies by these groups before the actual demonstration of their efficacy.

Apart from lung protective ventilatory strategies are there any other interventions that could potentially impact on ARDS mortality? The recent PROWESS study on the efficacy and safety of recombinant human activated protein C has implications for ARDS as well since sepsis remains not only the commonest trigger of ARDS but is also the commonest cause of death from ARDS.15 Sepsis and MODS was listed as the cause of death in only 18% of Vig’s series but this is at variance with international data where sepsis is overwhelmingly the commonest cause of death. Many of the PROWESS patients with sepsis had accompanying ARDS and it is therefore likely that this intervention could also reduce mortality in ARDS associated with sepsis. A landmark study by Van den Berghe showing that intensive insulin therapy conferred a distinct survival benefit to critically ill patients is yet another example of a general ICU study potentially impacting on ARDS survival as well.16 Another potential intervention has been the use of inhaled nitric oxide (NO). The data from four controlled studies of NO in ARDS have shown that although approximately 60% of ARDS patients will respond to inhaled NO, increasing their PaO2 by more than 20%, there is no evidence of translation of this physiologic benefit in oxygenation to improvement in survival.17 Finally the pro-inflammatory nature of conventional mechanical ventilation has refocused our attention on “unconventional” ventilation and respiratory support (high frequency jet ventilation, high frequency oscillatory ventilation, liquid ventilation using perfluorocarbons, ECMO) devices. Most of these studies have been too small and poorly designed to demonstrate any survival benefit however.

To conclude, these are exciting times for physicians practicing critical care medicine with a spate of recent studies showing that mortality in ARDS can be correctly predicted and survival eventually improved. It is to be hoped that these studies translate into direct benefit for our patients affected by ARDS.

REFERENCES

17. Klinger JR. Inhaled NO in ARDS. Crit Care Clinics 2002;45-68.