The prognosis of ARDS: appropriate optimism?

During the last 2 or 3 years, several reports have documented a marked and long-awaited improvement in the prognosis of the acute respiratory distress syndrome (ARDS). Early this year, Milberg et al. reported in the Journal of the American Medical Association [1] that fatality rates for 918 ARDS patients in their institution, after remaining as high as 53–69% from 1983 to 1987, declined steadily after that to reach a low of 40% in 1993. Even more impressively, the Berlin group [2] has reported an overall survival of 70% in 82 ARDS patients referred to their intensive care unit (ICU) since 1989. Morris et al. [3], using the “extracorporeal membrane oxygen (ECMO) criteria,” which were used during the 1970s to select a population of ARDS patients with a fatality rate of 90%, reported a mortality of “only” 60% in patients treated with mechanical ventilation (pressure controlled, inverted I/E ratio, reduced V_T etc.) or by using the extracorporeal CO₂ removal (ECCO₂R) technique. Hickling et al. [4] reported mortality to be as low as 26% in ARDS patients with an APACHE II predicted risk of 50%. A recent multicenter, randomized, placebo-controlled trial assessing the efficiency of aerosolized surfactant (Exosurf) in septic ARDS was recently completed [5]. Overall survival (in both treatment and control groups) was 60%. These exceptionally good results, obtained recently by several experienced groups, allowed Schuster [6] to produce a graph of the results of most of the large published trials on ARDS over 20 years, which showed that mortality has apparently declined steadily over time. When asked recently to comment on their results and explain the better survival they have obtained, the authors cautiously – due to the near absence of randomized studies and the historical nature of the available comparisons – proposed a slow, but definite, improvement in the efficacy of their treatments through many small and additive effects: pressure-controlled and/or inverted I/E ratio ventilation (Utah), reduction in V_T (New Zealand, and possibly Seattle), ECCO₂R and inhalation of nitric oxide (Berlin), prone positioning, better control of water balance and of nosocomial pneumonias, and use of corticosteroids in the late phases of the syndrome. Hence, a frank optimism?

However, before we are absolutely certain that we (or, at least, some of us) manage our ARDS patients better than we did 10 or 20 years ago, we have to demonstrate that we are treating the very same patients in terms of case mix, etiologies and co-morbidities, age, adjusted risks and number of organ failures, and that we use the same criteria and definitions. In the absence of randomized studies and a priori stratifications, which are rare in this syndrome as reviewed recently by Kollef and Schuster [7], similarities between historic groups are always difficult to demonstrate. Many factors, if not specifically taken into account, may induce large variations in otherwise apparently comparable series of patients. Age, for instance, has a strong impact on mortality in ARDS [1, 8, 9], as it does, more generally, in mechanically ventilated patients [10]. Accordingly, a series of young ARDS patients would certainly have a much better prognosis than a concurrent series of older patients, whatever treatment is given to both groups. Even the moment when a patient is declared a survivor is crucial: at discharge from the ICU or hospital, at 2 weeks, at 1 month, later? Sloane et al. [9] reported a mortality of 54% for their 153 ARDS patients at 5 weeks. Had an end-point at 4 weeks been chosen, the fatality would have been significantly lower, at 44%. Certainly, comparing series with different endpoints is hazardous and may lead to erroneous conclusions.
The degree of hypoxemia, usually expressed as the ratio of $P_aO_2$ over $F_iO_2$ ($P/F$), has an important, though ill-defined role. It would seem that extreme hypoxemia should carry the poorest prognosis. The reason that the ECMO trial had such a high mortality (i.e., 90%) may have been due to the highly selective criteria that were used: $P_aO_2$ < 50 mmHg with an $F_iO_2$ of 100%. Most of the recent trials, showing lower mortalities, also had more liberal criteria for hypoxemia: a $P/F$ < 150, 200, or even 300 mmHg. Knauss et al. [8] found that the mortality for the ARDS patients on their APACHE III database was higher when their initial $P/F$ was < 150 mmHg by comparison with those having a $P/F$ of only < 300 mmHg. But these patients also had a broad range of predicted mortality, with many of them at very low risk. Knauss et al. also found that in their series the predictive value of $P/F$ was much less than the more global APACHE index. Sloane et al. [9], comparing the mortality of ARDS patients from the same series but selected with three different ranges of $P/F$, did not find any difference. However, this factor should be more uniform in future studies if the recommendations of the American-European conference consensus are followed [11]. $P_aO_2$ reflects uniquely the degree of impairment of the gas exchange function of the lung, while the prognosis of ARDS depends also, if not predominantly, on other physiologic abnormalities, etiologies, co-morbidities, and associated organ failure. The weak correlation between low $P_aO_2$ and mortality may in fact suggest that our present techniques of respiratory assistance sustain successfully the vital functions of the most severely hypoxic patients.

By analogy to what has been shown in sepsis, patients who have in common only the vaguely defined ARDS most probably have very different prognoses. Knauss et al. [8] showed that the best predictor of mortality in ARDS was actually a global index, the APACHE III scoring system. In the population of 423 ARDS patients they selected from the APACHE III database, they showed also that there was substantial variability in the risk for hospital mortality. This approach has been used by Hickling et al. [4], who compared their own data and patient mortality with those predicted by the APACHE II system, raising the issue of the comparability of the New Zealand and American case mix. However, among the numerous factors constituting the APACHE score, those which designate specific organ system failures are probably the most important. Several reports have already shown that mortality increases in ARDS when other organ failures are added to lung failure [8, 12–14]. Bartlett et al. [12], analyzing the 713 patients considered for inclusion in the ECMO trial, noted that mortality was 40% when the lung was the only organ to fail and that it increased markedly when other organ systems failed. In a subset of patients with acute respiratory failure secondary to AIDS-related pneumocystic pneumonia, Montaner et al. [15] confirmed recently the specific importance of multisystem organ failures (MSOF) in predicting mortality. In our own series of patients (16), mortality was 92% in patients with initial MSOF ($n = 49$) and only 36% ($n = 22$) for those who had a single lung failure all along. Despite being heavily debated during the 1980s, the role of sepsis (initial or secondary) in causing MSOF is not yet clearly delineated, since MSOF may be present in ARDS without any evidence of sepsis. Ronco et al. [17] showed recently, for instance, that a hyperdynamic state present in ARDS did not necessarily correspond to a septic syndrome. Similarly, MSOF is frequently, but not always, associated with immunosuppression. But, whatever its cause, the addition of organ failure(s) other than lung failure is a good predictor of poor outcome. Again, this factor needs to be taken into account to compare survival of different populations of patients. Documentation of improvement in survival in ARDS should rely on the comparison of groups of patients similar in age, etiologies, co-morbidities, adjusted risk, organ failure, $P/F$ ratio, etc. Even if we now pay more attention to the description of patients when we publish outcome studies, historical comparisons will continue to be hazardous, since most of the information we feel it is necessary to collect was not recorded 10 or 20 years ago.

So, is our present optimism totally irrelevant? Probably not, since some of the publications already mentioned do provide strong evidence. Morris et al. [3], using the ECMO criteria, were able to select a group of patients very similar to those in the ECMO trial with significantly lower mortality (60% vs 90%). These figures were confirmed by Lewandowski et al. [2] in a subgroup of their ARDS patients that met the same criteria (67%). In reporting their impressive reduction in mortality within the last five years, Milberg et al. [1] give death rates after adjustment for age and etiology, for patients treated in the same institution and selected using the same definitions and criteria. Finally, it is probably fair to say that the prognosis for patients with a single lung failure has improved over time, possibly (hopefully?) due to better management. But we still fail to rescue those patients with MSOF, short of a treatment directed to these conditions. As far as the efficacy of the treatment of sepsis is concerned, Friedman et al. [18] recently noted that no progress was reported in that field from 1986 to 1993.