Surfactant Replacement Therapy in ARDS

To the Editor:

We read with interest the report in CHEST (October 2008) by Taut et al,1 in which a pooled analysis of five studies was performed where recombinant surfactant protein (SP)-C surfactant (Venticute; Nycomed; Roskilde, Denmark) was administered to patients with ARDS. No metaanalysis has demonstrated a survival benefit for surfactant administration in ARDS patients, but the reported studies had confounders such as dissimilar preparations, routes of administration, and doses. Many of these confounders were obviated by focusing on a single surfactant preparation that had been used with a similar protocol. The SP-C surfactant improved indexes of oxygenation, like many ARDS therapies, without altering mortality. However, in a post hoc analysis patients with direct ARDS caused by pneumonia or aspiration demonstrated a survival benefit.3

In contrast to adult and pediatric patients with ARDS, surfactant therapy is a valuable therapy in infants with respiratory distress syndrome.2 In infants, early treatment is more effective than later rescue therapy at reducing mortality.2 Taut et al,1 suggested (perhaps incorrectly1-4) that SP-C surfactant therapy was beneficial in patients with direct ARDS because more surfactant might be inactivated than in individuals with indirect ARDS. However, it would be important to know whether the apparent benefit in patients with direct ARDS was the result of lead-time bias. The very nature of patients with direct lung injury may have meant that they were recruited into studies at an earlier time point in their critical illness than those with indirect ARDS, but this does not appear to have been considered in the analysis.

It is clear that perturbations of surfactant quantity and function persist for many days in ARDS patients,2 and this appears to be worse in those with indirect ARDS.4 Moreover, in individuals with direct ARDS the failure to recover surfactant function was associated with death.5 All patients who were analyzed who had received SP-C surfactant treatment received only 24 h of therapy,1 and this may have greatly diminished the potential of this treatment to alter outcome.

Finally, one must recall that the protein fraction of surfactant comprises four molecules, two of which (SP-B and SP-C) reduce surface tension, while SP-A and SP-D have important immunomodulatory functions. These latter two proteins are members of the collectin family of host defense molecules, which bind microorganisms and modulate inflammatory cell function through chemotaxis and cytokine production. SP-D has been demonstrated to profoundly modulate inflammation in a hyperoxic model of acute lung injury.3 We would suggest that the best strategy for the application of exogenous surfactant in ARDS patients would be the early and prolonged use of a preparation containing more than one SP.

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2 Stevens TP, Sinkin RA. Surfactant replacement therapy. Chest 2007; 131:1577–1582

Response

To the Editor:

We appreciate the interest of Drs. Wise, Saayman, and Frost in our analysis of patients treated with a recombinant surfactant protein (SP)-C surfactant (Venticute; Nycomed GmbH; Konstanz, Germany).1 They note that the relatively early treatment of ARDS patients with surfactant may be associated with a better outcome and ask whether a lead-time bias might have influenced our observation that the outcome in patients with direct lung injury appeared to be better than that for patients with indirect lung injury.

We have compared the time from ARDS diagnosis to randomization (after which treatment was given within 2 h) for patients with direct or indirect lung injury. This mean (± SE) interval was 32.9 ± 1.3 or 26.5 ± 1.1 h (p = 0.0002), respectively. Thus, patients with direct lung injury, who appeared to have a better outcome, actually were randomized and treated 6 to 7 h later than those with indirect injury. Whether this difference is clinically relevant is unknown, but it appears that lead-time bias does not explain our observations. While we would also like to compare the time intervals from intubation to randomization (or treatment), this information is not available.

We caution against using published information, including that cited by the correspondents, to compare the time course of surfactant abnormalities in patients with direct lung injury vs those with indirect lung injury. Studies to date have included patients treated with tidal volumes >12 mL/kg body weight (volumes now known to be inherently injurious)2 and have not directly compared patients with direct or indirect lung injury. Future comparisons should require that patients be treated with a lung-protective ventilation strategy and that patients with direct or indirect lung injury be prospectively enrolled into a common study.

It is very likely that surfactant abnormalities persist for several days after the onset of either direct or indirect lung injury. Although our pooled analysis focused on only the first 24 h of treatment, study of the loss of exogenous surfactant from the lungs of treated patients has previously led us to suggest,3 as do the correspondents, that treatment extend beyond that period.

Composition of the ideal surfactant for treating patients with lung injury is unknown, and, in addition to either SP-C or SP-B...