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EDITORIAL

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Fluid management in ARDS: "keep them dry" or does it matter?

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Despite the fact that the Acute Respiratory Distress Syndrome (ARDS) has been recognized as a distinct clinical entity for more than 25 years, many – if not most – aspects of ARDS management are still controversial. Remarkably, there is not a single large randomized, prospective study which has shown any mortality *benefit* for any therapy [1–8].

As a result, what has emerged is some broad consensus on general issues (e.g. oxygen supplementation, hemodynamic support, nutritional support, antibiotics) and perhaps an emerging consensus (by no means uniform, and by no means based on solid clinical evidence) that mechanical ventilatory support should include lower tidal volumes, the least amount of positive end-expiratory pressure necessary to maintain oxygenation, a willingness to allow hypercapnia to develop if airway pressures are high, and the use of inverse ratio ventilation or other similar modes to salvage oxygenation when necessary. Despite the need to continue tests of new therapeutic agents, I strongly believe the recent experience in ARDS trials and in trials of patients at-risk for ARDS indicate a need to also re-evaluate the relative benefits of supportive therapies, since it now seems evident that large changes in outcome are unlikely to result from any one therapy.

A classic example of controversy still surrounding a supportive therapy is the continued debate over proper fluid management in ARDS. The justification for restricting fluid administration, or more directly, for actively trying to lower pulmonary capillary pressures is, of course, embodied in the familiar Starling equation. This equation predicts that whenever the permeability of the alveolocapillary membrane increases, lung edema develops at lower pulmonary capillary pressures than otherwise. Thus, the theoretical benefit of reducing pulmonary capillary pressures is *enhanced* not reduced, whenever membrane permeability is increased. Furthermore, an extensive animal experimental experience [9–21] supports the theoretical therapeutic benefit of reducing hydrostatic pressures during acute lung injury, including the use of diuretics to specifically reduce the amount of pulmonary edema, quantified as extravascular lung water (EVLW) [9–21].

Theory and experimental studies are also supported by clinical data, although until recently such studies were either very small or observational in design [22–26]. More recently, our group extended these clinical observations in a prospective, randomized trial of fluid management in patients with severe pulmonary edema, in which diuresis and/or fluid restriction (as clinically indicated or practically achievable) was emphasized [27, 28]. Of the 89 patients enrolled in the study, 50 had an initial wedge pressure less than 18 mmHg. There were 48 patients meeting formal criteria for ARDS or sepsis.

The principal evidence that the groups were actually treated differently with respect to fluid management as a whole was the difference in cumulative intake versus output (I-O). As expected, cumulative I-O was less in the group managed with the restrictive fluid strategy. Moreover, the differences in fluid management were greatest in the subset of 50 patients with a wedge pressure < 18 mmHg (mostly patients with ARDS or sepsis).

The initial EVLW (measured at the bedside by the thermal-green dye indicator-dilution technique) was not

significantly different between the two study groups, but EVLW was significantly less at each time point after 24 h in patients managed with diuresis/fluid restriction compared with the baseline value, which was not the case in the other set of patients. Patients from the group managed with diuresis/fluid restriction also required mechanical ventilation and were in the ICU for a significantly shorter period of time than patients from the other group. The time required for mechanical ventilation in the subset of patients with ARDS was also shorter for those managed with diuresis/fluid restriction.

Although ICU and hospital mortality were not different between the two management groups, the trends favored the group managed with diuresis and fluid restriction. Survivors (regardless of management group) had no net fluid gain on average, while non-survivors were characterized by positive rates of fluid gain. And for patients with $>15\%$ reduction in their EVLW and an underlying diagnosis of ARDS or sepsis, ventilator days and ICU days were less than those with $<15\%$ reduction in EVLW.

Thus, theoretical, experimental, and clinical data are all very consistent: EVLW accumulation is less and resolution is greater when clinical strategies are used that emphasize wedge pressure reduction or diuresis/fluid restriction. In patients with ARDS, these strategies are associated with less time on mechanical ventilation and in the ICU. However, no study has been large enough to demonstrate a statistically significant impact on mortality. Three recent editorials have all called for such a study to be performed [29–31].

On the other hand, fluid restriction or wedge pressure reduction could also plausibly worsen shock (commonly accompanying ARDS), whereas intravascular volume expansion might improve cardiac function. Fluid restriction might also worsen renal function, with its independent negative impact on outcome. Although patients in the diuresis/fluid restriction group of our study did show evidence of clinically mild worsening of renal function compared to the routinely managed patients [27], no difference in the number of patients requiring vasopressors or inotropic support, or the number of patient-days such therapy was administered, were noted. Furthermore, there was no difference in mean cardiac output, despite a statistically significant fall in the mean wedge pressure in the diuresis/fluid restriction group.

Even so, a strategy of relative or absolute fluid restriction for ARDS patients can certainly be misunderstood and abused. Fluid restriction and/or wedge pressure reduction in frankly hypovolemic patients is a prescription for clinical disaster, with vital organ hypoperfusion the expected adverse result. Thus, if one plans to embark on a strategy of keeping ARDS patients dry, it must be accompanied by careful clinical and/or invasive monitoring of organ function and hemodynamics, and the willingness to adjust therapy as necessary to maintain adequate perfusion. An unanswered question is whether perfusion, when threatened, should be principally maintained by adjustments in volume status or by the use of inotropes and vasodilators. Likewise, the end-point for choosing adequate perfusion when judging this primarily from hemodynamic data is unknown. Clinical trials of different endpoints, with different therapeutic strategies are needed. Better yet, alternative measures of adequate perfusion (besides lactate levels or mixed venous oxygen saturations) should be developed. At present, however, in the absence of data, we attempt to keep the wedge pressure as low as possible, and definitely below 12 mmHg, as long as systemic perfusion seems adequate. If stroke volume is low, we then use a combination of dopamine and dobutamine to increase stroke volume into the normal range. As of yet, we don't attempt to achieve supra-normal values. If the heart is dilated or stiff, as predicted by historical data or echocardiography, slightly higher wedge pressures are sometimes tolerated. In the presence of renal failure, we do not, as of yet, try continuous ultra-filtration or other such kidney replacement techniques simply to reduce the wedge pressure. When systemic hypotension requires vasopressors despite filling pressures >10 mmHg, we do not try to reduce the vasopressor requirement by pushing volume to achieve higher wedge pressure values.

The clinical strategy of fluid restriction/wedge pressure reduction may simply be a special case of strageties which seek to reduce *perfusion* to edematous lung units and to divert perfusion to better ventilated lung regions [32]. For instance, pulmonary venous resistance, and thus pulmonary capillary pressures, are probably elevated in many cases of ARDS, independent of filling pressures in the left heart. Thus, pharmacologic agents which lower pulmonary venous resistance, (for instance, thromboxane receptor antagonists), might have the same or even a greater effect on pulmonary capillary pressures without jeopardizing cardiac function. The relative benefits of such strategies, if any, compared with reducing intravascular volume and wedge pressure per se needs to be determined.

The molecular biology revolution offers great promise. But until that promise is realized, we must still focus on optimizing supportive care. In my opinion, it is cynical and misdirected to assume that all methods of providing such supportive care are equivalent. Indeed, recent evidence suggests that the mortality rate for ARDS has fallen significantly in the past decade [33]. If so, the reason can only be attributed to improvements in supportive care. At present, available data indicate that fluid management in ARDS patients can indeed affect outcome, and the optimal strategy is one in which the intensivist should attempt to achieve the lowest pulmonary wedge pressure consistent with an adequate cardiac output [34].

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