would be clinically relevant if serum sedative levels could be correlated to some aspect of titration of the agents—as we frequently do with antibiotics—but this is not the case with this class of drugs.

Regarding persistent delirium—whether it was related to sedation, another cause of delirium, or both cannot be determined from our study. For purposes of practicality, patients in our study were classified as persistent delirium when they scored as such up to 2 hours after sedative cessation. It is likely we have only identified a fraction of the reversibly delirious patients, given the limits of our before–after assessments. Accordingly, we believe that it is incorrect to infer from our data that the entity “persistent, sedation-related delirium” exists. Certainly, most of us have noted a scenario in which a patient emerges from delirium after several days of sedative interruption (more often when benzodiazepines are used). Although it would seem rational to categorize such a patient using the term “persistent sedation-related delirium,” our study did not evaluate such a scenario. Although an association may exist, our data cannot answer the question of whether residual sedatives (which certainly could contribute to persistent delirium) are the cause of poor outcomes or merely epiphenomena. Such a question is very difficult to disentangle, because residual sedation leads to longer ventilator days, longer intensive care unit (ICU) length of stay, immobilization, etc., all of which lead to poor ICU outcomes.

There are no established treatment options for ICU delirium. Unfortunately, pharmacological interventions (e.g., haloperidol [4], rivastigmine [5]) to date have been unsuccessful. It is not likely that ICU delirium, with such a wide array of underlying causes, will have a single treatment that will be universally successful. Accordingly, prevention of delirium (e.g., early mobilization, sleep preservation, avoiding deliriogenic drugs) may be the best solution. We agree that sedative minimization, daily sedative interruption, and/or a sedation algorithm should be universal in ICU practice (6). Furthermore, we believe our data clearly show that screening tests for delirium, such as the Confusion Assessment Method for the ICU, should be changed and performed after sedatives have been stopped to ensure the best accuracy.

We thank Dr. Ely for his interest in our study and the important questions he raises. We suggest the persistent and mixed delirium patients were sicker because of more sepsis and hypoxemic respiratory failure, despite similar Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Our findings regarding persistent and mixed delirium essentially repeat the seminal work done by his group a decade ago (7). The most important new finding in our trial is that 12% of patients were miscategorized as having delirium with a poor prognosis if the sedative interruption was not performed. Therefore, we agree that these data suggest that delirium evaluations must be performed without the veil of sedation (i.e., after sedative interruption); certainly, performing the evaluation also before sedative interruption seems optimal, and it may be useful to consider modification of recent guidelines (6). As outlined in our response to Pandharipande and colleagues above, we do not think that serum drug levels likely would shed light on the question of different types of delirium. Regarding the question of analyses in light of concomitant presence of sedation and sepsis, we actually did perform an interaction analysis. Our article states: “Of the 218 pre-DIS [daily interruption of continuous sedation] observations scored as delirium, 63 (28.9%) had paired post-DIS observations that were scored as normal. Subjects were 10.5 times (95% confidence interval, 5.3–21.0; $P < 0.001$) more likely to be classified as delirium when assessed before sedation interruption compared with after sedation interruption. This

remained true after adjusting for baseline and admitting characteristics (e.g., study day, age, APACHE II, sex, diagnosis, hypertension, liver failure, kidney failure, antibiotic, corticosteroid and vasoactive drug use [OR = 11.05; 95% confidence interval, 5.45–22.39; $P < 0.001$]).” Sepsis was one of the diagnoses in the model; although we did not explicitly state this in the manuscript, sepsis did not significantly impact the pre/post daily interruption of sedation results. ■

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Importance of the Kidney, Vessels, and Heart with Administration of β_2 Adrenergic Receptor Agonists in Patients Susceptible to Acute Respiratory Distress Syndrome

To the Editor:

We read with great interest the recent article by Perkins and colleagues demonstrating that the administration of a β_2 -adrenergic agonist did not improve clinical outcomes but did result in lung fluid clearance in patients undergoing elective esophagectomy (1). This is one of several studies that have demonstrated a decrease in lung water after the administration of a β -agonist in patients with, or susceptible to, acute respiratory distress syndrome (ARDS) while finding no differences in clinical outcomes between drug and placebo (2, 3). Stimulation of the β_2 -adrenergic receptors (β_2 ARs) has been shown to result in lung fluid clearance, primarily through two distinct pathways:

alveolar fluid clearance and relaxation of the pulmonary lymphatics (4). In animals, there is increased lung fluid clearance in response to circulating catecholamines to improve lung diffusion and gas exchange. This lung fluid clearance mechanism initially occurs with birth and carries on through adulthood such that stimulation of the β_2 ARs results in activation of epithelial Na^+ and Cl^- channels, which ultimately enhances the removal of fluid. Several important cell and animal studies have confirmed the importance of this β_2 AR pathway on lung fluid clearance. Along these lines, as mentioned in the article by Perkins and colleagues, salmeterol has been shown to reduce the incidence of high-altitude pulmonary edema. In addition, β -blockade results in lung fluid accumulation after rapid fluid loading when combined with exercise (5). We have previously demonstrated that rapid fluid loading (30 ml/kg) results in lung fluid accumulation that is dependent on genetic variation of the β_2 ARs (6). In addition, we have demonstrated that normobaric hypoxia results in lung fluid clearance (as determined through CT scanning, assessment of pulmonary function, and assessment of lung diffusion for carbon monoxide and nitric oxide) that is dependent on the amount of β_2 ARs on lymphocytes (7). Collectively, these data demonstrate the importance of the β_2 ARs on lung fluid regulation in humans.

Despite this important effect of β_2 AR stimulation on lung fluid clearance, several studies have failed to demonstrate improvements in clinical outcomes (primarily mortality, ventilator-free days, and length of hospital stay) after the infusion or inhalation of short- and long-acting β -agonists (1, 2, 8, 9). Despite this lack of improvement in clinical outcomes, some of these studies have demonstrated a decrease in lung water with the administration of a β -agonist (1–3). We feel that there may be an important effect of these receptors on the kidney leading to this lack of improvement in clinical outcomes, along with alterations in cardiovascular function. In addition to our previous work demonstrating lung fluid accumulation that is dependent on genetic variation of the β_2 AR, we have also found that renal sodium (Na^+) handling after rapid fluid loading was dependent on this same genetic variation. These studies, along with many before them, demonstrate the importance of β_2 ARs on renal Na^+ reabsorption in humans. It is not surprising that the same pathway that results in lung fluid clearance (or Na^+ absorption from the lung to the blood) is important in renal Na^+ handling (or Na^+ absorption from the kidneys to the blood); this conservation of a pathway that does the same thing in two different organs plays an important role in evolution. Toward this end, β_2 ARs have been localized to the inner-medullary collecting duct and are thought to play a role in “fine-tuning” of renal Na^+ handling. In support of this theory and related to the present study, at least one study published cumulative fluid balance data and demonstrated that the administration of albuterol resulted in a greater cumulative fluid balance when compared with placebo (8). Previous research has suggested that negative fluid balance is important in reducing mortality in patients with acute lung injury (10), and it has been established that conservative fluid management strategies are important in patients with ARDS (11). In their study, Perkins and colleagues do, in fact, state that they used a “fluid-conservative hemodynamic approach.” What is missing from our current understanding of β_2 AR agonists in ARDS is data on renal Na^+ handling (urine Na^+ , fractional excretion of Na^+ , etc.), which may allude to possible small differences between drug and placebo that may be important on clinical outcomes. It may seem unlikely that the

administration of an inhaled drug can have an effect on the kidneys; however, we have recently observed that the administration of inhaled amiloride (which inhibits epithelial Na^+) blocks lung fluid clearance and results in an unexpected but dramatic diuresis in healthy subjects exposed to normobaric hypoxia.

We have also demonstrated that the inhaled administration of albuterol (nebulized 2.5 mg in 3 ml normal saline) leads to an increase in cardiac output secondary to smaller increases in heart rate and stroke volume in healthy humans (12). In this same study we also demonstrated a drop in systemic vascular resistance and mean arterial blood pressure with albuterol. We hypothesize that the increase in heart rate in this study was secondary to a drop in blood pressure (that occurs through stimulation of the β_2 AR on the vascular walls resulting in vasodilation and a drop in systemic vascular resistance) rather than through direct stimulation of these receptors because the β_1 -adrenergic receptors are the primary receptor involved in the chronotropic control of the heart. This may also explain why more subjects on a β_2 AR receive vasopressors, when compared with placebo, in previous studies (8). In contrast, 20% of the ventricular wall is comprised of β_2 AR, and it is therefore plausible that the administration of these drugs results in increased cardiac output through direct increases in stroke volume. Therefore, there are possible important interactions between cardiovascular alterations and renal Na^+ handling that should be further studied with this class of drugs.

To summarize, it is clear that the administration of a β -agonist results in lung fluid clearance, but, on average, there has been no positive effect on clinical outcomes in patients susceptible to ARDS. It has been hypothesized that this is due to cardiovascular changes after the administration of a β -agonist. Although this may play a role, it is also possible that the administration of an inhaled β -agonist stimulates renal Na^+ reabsorption, causing fluid retention, which can be detrimental to patients with ARDS but not in other conditions in which the administration of these drugs has been shown to increase lung fluid clearance and improve clinical outcomes. It is possible, therefore, that a more aggressive diuretic strategy is needed while administering a β -agonist. ■

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Reply

From the Authors:

We thank Drs. Snyder and Johnson for their insightful interest in our recent trial article (1). We agree with them that there are many potentially important nonbronchodilator effects of β -agonists, including stimulation of alveolar fluid clearance, effects upon inflammatory cells, and potentially promoting alveolar epithelial repair responses via MMP-9 (2–5). The wealth of supporting data from translational and animal/preclinical studies drove the hypothesis that β -agonists might work as a therapeutic or preventative agent in patients with or at risk of acute respiratory disease (ARDS). Unfortunately, as has been so often the case with developing new strategies for therapy in ARDS, translation of these findings into clinical benefits has been unsuccessful, with the BALTI-2 study finding an increased risk of death in patients with ARDS treated with intravenous β -agonists (6).

In their elegant discussion, Snyder and Johnson suggest that deleterious effects of β -agonists upon the kidney may have counteracted any beneficial effects of β -agonists upon alveolar fluid clearance in patients with ARDS. We agree that the effects of β_2 -agonists upon renal sodium handling are important to

consider. We reported no difference in daily fluid balance in the phase 2 BALTI-1 paper (7) but have no additional unpublished data from BALTI-2 (6) or BALTI-prevention (1) to help shed light on this action. However, we note that when intravenous β_2 -adrenergic agonists were used for tocolysis during pregnancy, they have been associated with reduced sodium, potassium, and water excretion, leading to a reduced hematocrit and intravascular hypervolemia (8, 9) and development of maternal pulmonary edema (10).

Finally, we suggest that, although our BALTI-prevention trial did not reduce the incidence of ARDS, we did demonstrate some findings worthy of future study. We found that inhaled salmeterol resulted in a reduction in systemic inflammation, which resulted in reduced alveolar epithelial barrier dysfunction perioperatively. The magnitude of the effects was not sufficient to prevent postoperative ARDS but did significantly reduce the incidence of reported postoperative pneumonia.

We suggest, therefore, that salmeterol protected the alveolar epithelium in patients undergoing esophagectomy by reducing inflammatory and epithelial damage during injurious one-lung ventilation. We agree with Snyder and Johnson that combination therapies, targeting different mechanisms implicated in the development of ARDS, are likely to be needed to successfully treat and prevent ARDS. ■

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