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Reply: β_2-Agonists and Acute Respiratory Distress Syndrome

*From the Editorialists**:

In their letter, Snyder and Johnson propose a mechanism to explain why the clinical trials evaluating β_2-agonists as a treatment or preventive therapy for acute respiratory distress syndrome (ARDS) have failed. They suggest that extrapulmonary effects of β_2-agonists on renal Na^+ handling and the cardiovascular system might have caused an increase in total body water content, offsetting their beneficial effects on alveolar fluid clearance. Activation of β_2-adrenergic receptors (β_2ARs) may lead to increased total body water content by decreasing renal Na^+ excretion (1). In addition, engagement of β_2ARs on the vasculature may cause a drop in systemic vascular resistance, necessitating the increased administration of fluids and an increase in total body water content.

Several factors argue against this hypothesis. Although the systemic administration of β_2-agonists in the BALTI 2 trial (2) may have affected renal Na^+ handling and cardiovascular responses, the inhalation administration of β_2-agonist is unlikely to have done so (3–5). Indeed, Perkins and colleagues found that β_2-agonist therapy decreased extracellular lung water content in a subgroup of patients receiving inhaled β_2-agonists in the BALTI prevention trial (4). Snyder and Johnson point out that patients receiving β_2-agonist therapy received more cumulative fluids compared with those who did not in the ALTA trial (2,988 $\pm$ 6,614 ml in the albuterol group vs. 1,905 $\pm$ 6,388 ml in the control group; not significant) (5). Although this may be due to the effect of β_2-agonists on renal Na^+ excretion and caon the rdiovascular system, this disparity more likely reflects the inclusion of more patients with shock in the ALTA trial compared with the previous study (approximately one half vs. one third) (5, 6).

In summary, we agree with Johnson and Snyder that many mechanisms likely play a role in the unexpected outcomes with the use of β_2-agonists for the treatment or prevention of ARDS (7). However, we think the bulk of the evidence from these trials and others suggests that β_2-agonist therapy reduces lung water content. Despite this improvement, these agents failed to improve or prevent ARDS. Perhaps this is because only a fraction of patients with ARDS die directly as a result of hypoxemia. The majority of deaths occur due to development of multiple organ dysfunction, and only patients with severe ARDS benefit from therapies improving oxygenation (8, 9). Alternatively, the activation of β_2ARs in other cells in the lung may negate the beneficial effects of their activation in the alveolar epithelium. For example, we have recently shown that β_2-agonist therapy worsens lung inflammation in a murine model of lung injury via engagement of β_2ARs on macrophages (10). We agree with the authors that additional studies will be needed to distinguish the beneficial effects of β_2ARs from their unwanted and harmful effects. ■

*Drs. Budinger and Mutlu wrote an editorial (7) on the article by Perkins *et al.*

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