RETURN TO THE EDITOR: We recently demonstrated that variation in the gene that encodes the β2-adrenergic receptor (β2AR) differentially influences lung fluid accumulation in response to rapid saline loading in healthy humans (4). The main point presented by Dr. Eisenhut (1) is that the cystic fibrosis transmembrane conductance regulator (CFTR) may play as important, if not a more important, role in β2AR-mediated lung fluid regulation. Although it was not possible from the methods used in our paper to determine which mechanism of lung fluid regulation dictated the differences in lung fluid accumulation between the genotype groups, we concluded that the most likely reason for the observed differences in our study resulted from β2AR-mediated relaxation of the pulmonary lymphatics. We also discussed other possible mechanisms involved in lung fluid clearance, primarily the β2AR regulation of the epithelial Na+ channel (ENaC) on alveolar cells.

Because the CFTR is also regulated by cAMP it is possible that increases in receptor density or function observed in Gly16 group could result in alveolar fluid clearance via a CFTR pathway (5). Previous studies demonstrated a role of CFTR in β2-stimulated lung fluid reabsorption, with most highlighting an important interaction between CFTR and ENaC. An elegant study by Fang et al. (2) demonstrated the importance of CFTR in stimulated, but not basal, lung fluid absorption in the intact mouse and human lungs. In another study, Fang et al. (3) concluded that the activity of ENaC likely results in a depolarization of alveolar type II cells that augments Cl− absorption through CFTR. Specifically, when amiloride is applied to alveolar type II cells (decreasing the activity of ENaC) Cl− transport across the alveolar cells is lower. It is true, however, that CFTR inhibition alone (using CFTRinh-172) decreases cAMP-mediated increase in lung fluid reabsorption but to a lesser degree than amiloride. Clearly, there is an effect of inhibition of CFTR on lung fluid reabsorption, under β2AR-stimulated conditions; however, given the previously determined importance of the ENaC in alveolar fluid clearance, the inhibition of basal lung fluid reabsorption with amiloride but not CFTRinh-172, and the synergistic effects of ENaC activity and CFTR in lung fluid reabsorption, it is difficult to conclude that one mechanism of alveolar fluid clearance is more important than another.

We agree with Dr. Eisenhut (1) that the CFTR activation appears to play an important role in lung fluid regulation. However, in the present study it is not likely that there was significant alveolar flooding, and it is less likely that the clearance of fluid from the alveolar air space played an important role in the genotype-related differences; more likely would be differences related to interstitial fluid regulation. Additional work is needed to determine the importance of alveolar fluid clearance mechanisms in humans, as well as the contributions of the ENaC and CFTR relative to these genotype groups.

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