measures, in well-defined anatomical regions, the total amount of gas entering in previously nonaerated and poorly aerated regions. Therefore, this method roughly measures the same entity of the lung mechanics-based methods.

In conclusion, if the target is the measurement of the amount of pulmonary units, which likely undergo opening and closing at PEEP below 15 cm H_2O, the only method available is the computed tomography scan at threshold −100 HU (−200 HU could be tolerated). In contrast, if the target is the measurement of the total improvement of aeration, resulting from gas entering in the previously nonaerated regions and in the already aerated regions, the Rouby's method and lung mechanics–based methods are indicated. Therefore, the problem is not whether one method is better than the other but rather what we want to measure. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Apneic Oxygenation Has Not Been Disproven

To the Editor:

I read with interest the article on apneic oxygenation by Semler and colleagues (1). I argue that the study was severely underpowered to detect any clinically significant difference between the two study arms, and the negative findings are thus hardly surprising.

First, when a procedure is mostly safe, and the goal is to prevent rare catastrophes, median outcomes do not show the whole picture. Indeed, the median lowest arterial oxygen saturation was 90% in the usual care arm, which would have required an utterly implausible median lowest saturation of 95% in the intervention arm just to reach prespecified statistical significance.

Second, the authors did observe a huge difference (15.8% vs. 25.0%) in the incidence of saturation lower than 80% between the two groups. If this difference of 10% is real, it would obviously be clinically relevant. Statistical significance was not attained, however, simply because the sample was too small. If we were to design a trial to verify that this difference in proportion is real, a study of 150 patients would achieve a power of only 28% to detect a difference; 312 patients in each arm would be required to demonstrate a difference with the usual β of 0.2.

To state the same point in another way, in this study sample of 150 patients, when the usual care is associated with an incidence of 25% of saturation lower than 80%, apneic oxygenation needed to reduce this percentage to 8% or lower before achieving statistical significance; that is, the study was only powered to detect a difference of at least 17% in the rate of severe desaturation (or a proportional reduction of 68%).

Given these statistical limitations, a more rigorous conclusion would have been that apneic oxygenation does not seem to increase the mean lowest arterial oxygen saturation; it does not reduce the incidence of desaturation by more than 68%, although smaller reductions cannot be excluded. ■

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Reply

From the Authors:

We appreciate the interest demonstrated by Dr. Pavlov, and the airway management community in general (1), in our randomized trial of apneic oxygenation during endotracheal intubation of critically ill adults (2). Dr. Pavlov's primary concern is the power of our trial. Our sample size (150 patients) was selected using the same primary endpoint (lowest arterial oxygen saturation) and minimum clinically meaningful difference between groups (5%) as prior high-quality trials targeting desaturation during endotracheal intubation (3, 4). We observed a numerical difference in lowest oxygen saturation between the apneic oxygenation and usual care arms of just 2%, well short of clinical or statistical significance.

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This was true despite nearly half of the patients in each arm experiencing lowest oxygen saturations in the 60s, 70s, and 80s, which are sufficient rates of desaturation for apneic oxygenation to have conceivably had an effect. As Dr. Pavlov correctly asserts, however, our trial was not powered to make inferences regarding less common secondary outcomes, such as the incidence of lowest oxygen saturation less than 80%. Although we respectfully resist Dr. Pavlov's proclamation of "a huge difference (15.8% vs. 25.0%) in the incidence of saturation lower than 80% between the two groups" (referring to six total patients), and his assertion that "statistical significance was not attained … simply because the sample was too small" (reliant on the flawed assumption that small differences in one of many secondary outcomes would persist in a larger sample), we agree with his overall point. The relationship between immediate complications of endotracheal intubation and long-term, patient-centered outcomes remains incompletely understood. If only the most extreme desaturations are of clinical importance, then our trial (and most other emergent intubation trials) would be vastly underpowered. Future research should empirically examine which surrogate endpoints most closely relate to patient-centered outcomes such as cardiac arrest and death. Future trials should also consider larger sample sizes to target increasingly robust surrogate endpoints or clinical outcomes.

Finally, Dr. Pavlov titles his letter "Apneic Oxygenation Has Not Been Disproven." The interventions we apply to our patients should be proven to be effective, not presumed effective until proven otherwise. Despite being promoted by experts for half a decade (5) and administered to thousands of patients across the world, before our trial apneic oxygenation during intubation outside the operating room had never even been tested, much less proven. We applied apneic oxygenation in the manner recommended (nasal cannula set at 15 L/min [6]) to the patient population recommended (all patients being intubated, including those receiving noninvasive ventilation or bag-valve-mask ventilation [6]) and did not find it to be effective. This suggests, at a minimum, that the effect of apneic oxygenation on desaturation during emergent intubation is not as great as we had previously hoped. We readily acknowledge that our trial was just one trial of one method of delivering apneic oxygenation to one patient group. Although our results agree with another recently published trial that failed to demonstrate a benefit of apneic oxygenation at 60 L/min among patients with hypoxic respiratory failure (4), different patient or operator populations may produce different results. If, in the future, a high-quality trial (large, randomized, concealed-allocation, high compliance with the assigned intervention, minimal missing data and loss to follow up, and objective data collection of a clinically meaningful outcome) demonstrates apneic oxygenation to be effective in a specific context, we will eagerly employ it in that context. Until then, we will shift focus away from apneic oxygenation and toward airway management interventions proven to help patients. ■

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Erratum: Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and Cystic Fibrosis Patient Registry Data

There are errors in an article by Sawicki and colleagues (1), which appeared in the October 1, 2015, issue of the *Journal*.

In the Results: Effect of Ivacaftor on Lung Function section (p. 838), the corrected first sentence of the last paragraph should read: "Sensitivity analyses using Knudson and colleagues (25) predicted formulas resulted in a more significant slope difference between groups (*see* Table E1 in the online supplement)." The original omitted the word "slope." In the Results: Effect of Ivacaftor on BMI-for-Age *z* Score section (p. 838), the corrected last line should read: "The initial treatment effect detected at index was maintained at 3 years, at which point the estimated BMI *z* score was 0.087 (SE $\pm$ 0.08) in the *G551D* ivacaftor group and -0.23 (SE $\pm$ 0.04) in the *F508del* control group ($P < 0.001$)." The original misstated the *P* value as $P < 0.01$.

In the Discussion section, in the sixth paragraph (p. 841), the corrected second sentence should read: "The CFFPR data is only for U.S. patients with CF, whereas the ivacaftor trials included in these analyses were conducted throughout the United States, Canada, Europe, and Australia, where children and adolescents with CF