Avoiding bias in the annualized rate of changed of FEV1

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reasonable to conclude that if PSR inhibition occurred at a higher PaCO₂ during PLV than GV, then pulmonary stretch must have been higher during PLV than GV. That is, PSR activity was inhibited during PLV at a higher pressure than during GV since PaCO₂ was high during PLV.

In addition, since the model studied by Sindelar and coworkers was a small lung lavage–injured cat (2.3 ± 1.0 kg), it is unlikely that the impact of perfluorocarbons on dependent lung would be the same as in an adult human. The difference in the height of the lungs (about 3 to 4 cm vs. 15 to 20 cm) would result in marked differences in the effect of the perfluorocarbon on dependent alveoli. Considering the quantity of perfluorocarbon instilled in adult patients (30 ml/kg or about 2,250 ml, 75 kg adult) versus the studied cats (30 ml/kg or about 69 ml, 2.3 kg) and a perfluorocarbon density of 1.9, it is difficult to conceive that the most gravity-dependent alveolar pressure during both inspiration and expiration would be similar during GV and PLV at the same airway gas pressure.

It is important to remember that, during PLV, gas ventilation is provided on top of the perfluorocarbon-filled lungs. It is true that with gas ventilation the perfluorocarbon spreads over a larger lung area. However, there is still a column of fluid on top of dependent alveoli that is pressurized by the gas ventilation. Overall, what is clearly needed is additional research into the mechanisms of dependentalveoli that is pressurized by the gas ventilation.

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From the Authors:

We thank Dr. Quanjer and colleagues for their insightful response to our recent article (1). We agree that any study that looks at lung function decline is inherently biased; one cannot measure lung function in a dead person, and people who develop health problems are probably less likely to participate in studies or to show up for follow-up (1). In addition, it has been demonstrated that both the intra- and interday variability in lung function can be as high as 8% (2).

The purpose of our analysis was not to determine rates of normal lung function decline in this population but rather to see if being a “rapid decliner” resulted in adverse outcomes. We stratified our cohort to compare the quartile with the most rapid decline to the other three quartiles. This approach would, hopefully, decrease the influence of the bias that Dr. Quanjer and colleagues suggest is present. In a new stratified analysis of these data in response to Quanjer and colleagues’ letter, the risk of being in the rapidly declining quartile for mortality was similar in the 44–49-year-olds (hazard ratio [HR], 1.6; 95% confidence interval [CI], 0.9, 2.7) and the 60–66-year-olds (HR, 1.5; 95% CI, 1.2, 1.9), suggesting that any bias introduced by our classification strategy did not influence the outcome.

The comment that a 3-year interval was “too short to accurately estimate longitudinal decline” raises a separate issue. How exactly do people lose lung function? While across a population the mean annual loss of FEV$_1$ may be 30 ml, it is pretty unlikely that people wake up each day with an FEV$_1$ that is 0.1 ml less than what it was the day before. It is more likely that discrete events result in acute decreases in lung function, followed by a partial or complete recovery of that function (3). In the setting of a person with established chronic obstructive pulmonary disease (COPD), we would call that event an exacerbation, but in a person with no diagnosis or normal lung function we might call this event a lower respiratory infection, flu syndrome, or something similar. In addition, many other conditions, such as congestive heart failure, diabetes, and obesity, can affect lung function both acutely and chronically (4). Of note, in our study, people who had normal lung function at baseline but were in the rapidly declining group at 3 years had significantly higher mortality during follow-up (1). Thus, our estimate, though imprecise, was a marker for adverse outcomes.

In an ideal world, the study of how lung function changes over time and influences outcomes includes a population where all study participants show up, don’t get sick or die, produce high-quality and reproducible tests, and don’t have comorbid conditions that might influence their results. Of course, in the world in which we conduct research and see patients, none of these conditions apply, and limiting our research to subjects who meet these conditions may not provide the information we need to better understand diseases such as COPD and improve how we care for our patients.

Conflict of Interest Statement: D.M.M. serves on Advisory Boards for Boehringer Ingelheim, GlaxoSmithKline (GSK), and Ortho Biotech. He is on the speaker’s bureau for Boehringer Ingelheim, GSK, and Dey. He has received research grants from GSK and Pfizer. M.M.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.J.D. is a current employee of GSK R&D and owns GSK stock options.

References