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Reply to Macklem and Irvin

Ronald L. Sorkness

School of Pharmacy and Departments of Medicine and Pediatrics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin

TO THE EDITOR: We thank Drs. Macklem and Irvin (3) for their comments, and for their insights regarding the 1996 paper coauthored by Dr. Macklem (2). As noted in our paper (4), the study by Gibbons et al. (2) was the first to introduce the concept of partitioning the forced expiratory volume in 1 s (FEV_1) in the context of a response to aerosolized histamine, and the first to report an association between a histamine-induced reduction in forced vital capacity (FVC) and a history of asthma instability. These were important findings that, as noted in our paper (4), were concepts on which we based our analyses of baseline obstruction in severe asthma. Our study developed further the concept of partitioning the FEV_1, demonstrating mathematically that this may be applied to an analysis of baseline obstruction, and we employed this approach to compare patterns of air trapping relative to airflow limitation in severe vs. nonsevere asthma in a large cohort that was fortified with subjects meeting the American Thoracic Society (ATS) Workshop classification for "Severe Asthma" (1). In their letter, Drs. Macklem and Irvin (3) challenge the originality of our results, suggesting that our conclusions had already been established by the paper of Gibbons et al. (2); however, there are several original aspects of our paper that were not recognized by Drs. Macklem and Irvin.

Most importantly, the Severe Asthma Research Program (SARP) data set is unique. The cohort used for our study included 669 nonsmoking adults with asthma, 43% of whom met the ATS Workshop criteria for Severe Asthma. These numbers provided an unprecedented opportunity to explore the characteristics of predefined populations of severe and nonsevere asthma with adequate power to discern distinct patterns within these broadly defined classifications. In contrast, it is unlikely that there was a substantial number of subjects in the Gibbons cohort that would have been classified as "Severe" by the ATS Workshop criteria, in that baseline airway obstruction and air trapping, prevalent in the SARP Severe Asthma group, was largely absent from the Gibbons cohort, which had minimal baseline obstruction [FEV_1 99 ± 14 (SD) %predicted], and no apparent baseline air trapping [FVC 106 ± 14 (SD) %predicted, similar to that of the non-asthma group in SARP, 103 ± 12 (SD) %predicted]. About one-half of the subjects in the Gibbons cohort were current smokers, which may have introduced an additional variable that was absent in the SARP cohort. Baseline airway obstruction in predefined severe vs. nonsevere asthma was the primary focus of our analysis of the SARP cohort, in contrast to the Gibbons focus on histamine responsiveness in a cohort of asthmatic subjects without baseline obstruction. Thus the two studies addressed different questions in different populations.

Although Gibbons et al. (2) presented the idea that a change in FEV_1 might be partitioned into the accompanying changes in FVC and FEV_1/FVC, the quantitative aspect of their analysis was limited to the percent decrease in FVC associated with a 20% decrease in FEV_1. They did not do a mathematical confirmation of their idea, and their implication that the concomitant percent decrease in FEV_1/FVC would be equal to 20 minus the FVC percent decrease is approximately, but not mathematically, accurate. We developed the idea further, deriving equations that provide a mathematical foundation for the partitioning of FEV_1, not only in the context of a change during bronchoprovocation, but also for patterns of baseline obstruction. We believe this to be original. Our results showing differences in the patterns of baseline air trapping relative to baseline airflow limitation in the two defined asthma populations also are original. Our paper complements and extends the ideas and results presented by Gibbons et al. (2) in 1996; we hope that it refreshes interest in exploring patterns of airway obstruction and asthma phenotypes.

Address for reprint requests and other correspondence: R. L. Sorkness, 777 Highland Ave., Madison, WI 53705 (e-mail: rlsorkne@wisc.edu).

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Dividing the FEV_1 into its component parts

Peter T. Macklem[1] and Charles G. Irvin[2]

[1]*Meakins-Christie Laboratories, McGill University Health Centre Research Institute, Montreal, Quebec; and* [2]*Department of Medicine, University of Vermont, Burlington, Vermont*

TO THE EDITOR: Sorkness et al. (1) show that the forced expiratory volume in 1 s (FEV_1) expressed as percent predicted can be broken down into its two components, forced vital capacity (FVC) and FEV_1/FVC, also expressed as percent predicted. They claim that "this is a novel approach [for partitioning the FEV_1] in a quantitative manner". In fact, this quantitative novelty was introduced 12 years ago by Gibbons et al. (2) for exactly the same reason that Sorkness et al. (1) use it: to detect asthmatic subjects with severe disease. Sorkness et al. suggest that severe asthmatic subjects may be fundamentally different from nonsevere asthmatic subjects in that they have airway closure, causing gas trapping, and this can be detected by a lower FVC in the severe group. If so, the frequency distribution of fall in FVC at the dose of agonist producing a 20% decline in FEV_1 (PC_{20}) should be bimodal. However, Gibbons et al. (2) found that in 146 asthmatic subjects, this distribution was unimodal and normally distributed. It could be claimed that the numbers were insufficient to demonstrate bimodality, but 64 of the 146 patients had a fall in FVC $\geq$ 15%, accounting for 75% or more of the fall in FEV_1.

Curiously, in a control group of only 20 healthy subjects receiving high-dose methacholine challenge, there was clear evidence of bimodality: 16 subjects had a fall in FVC ranging from 0 to 15% and there were none between 15 and 19.9% but 4 between 20 and 55%. Could it be that these four subjects were at risk for developing asthma?

Sorkness et al. (1) did not report the fall in FVC at the PC_{20}, and their subjects were preselected as either severe or nonsevere asthma. This selection would prevent detection of bimodality; an unselected group of patients like those studied by Gibbons et al. (2) would be required. Sorkness et al. (1) claim that their study "is the first . . . to show the predilection of severe asthma for air trapping over the entire range of airflow limitation," but the asthmatic subjects studied by Gibbons et al. had a mean baseline value of FVC and FEV_1 of 105.7% and 98.9% predicted, respectively, with lower 95% confidence limits of 76.9% and 70.1% predicted, respectively, so the claim of Sorkness et al. to originality can be challenged. Finally, Gibbons et al. found no correlation between PC_{20} and percent fall in FVC at the PC_{20}, proving that sensitivity to methacholine and response to the agonist are unrelated phenomena.

Address for reprint requests and other correspondence: P. T. Macklem, P. O. Box 250, Lansdowne, Ontario, Canada K0E 1L0 (e-mail: peter.macklem@gmail.com).

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