result that FRC/TLC and RV/TLC ratios are disproportionately elevated.

We have speculated about the influence of erroneously elevated volume ratios on the interpretation of published COPD outcome studies. For example, Fessler et al.² developed a model in which plethysmographically measured RV/TLC ratios predicted improvement in FEV₁ following lung volume reduction surgery (LVRS). Because any plethysmographic error would be proportionately greater for RV, the RV/TLC ratio would be artificially elevated. Among LVRS candidates in our sample, average plethysmographic RV/TLC was 64.9%, whereas average helium dilution RV/TLC was only 38.4%. When incorporated into the model of Fessler and colleagues, this difference in RV/TLC yields a two-fold difference in predicted post-LVRS improvement in FEV₁ (30% for plethysmographic vs 15% for He estimates). Also, the data of Casanova et al.³ indicated an approximate 5% annual increase in mortality for each 1% decrement of IC/TLC ratio in COPD. Among our subjects, plethysmographic IC/TLC averaged 20.7%, whereas helium IC/TLC averaged 27.6%. This difference in the estimate of IC/TLC ratio yields an approximate 30% difference in predicted annual mortality. We believe these examples demonstrate potential consequences of plethysmographic error for predicting clinical outcomes and indicate the need to take a new look at an accepted measure.

With respect to the observed lack of significant association between TLC and degree of airflow obstruction in the study of Dykstra et al.,¹ we point out two things. First, the authors used a conservative criterion of P < .01 for inclusion of TLC predictors in the statistical model: The actual P value for the association of TLC and FEV₁ in their multivariate model was 0.04. Second, we observed a threshold effect in the relationship between FEV₁ and plethysmographic overestimation of TLC such that the magnitude of apparent error became much greater at FEV₁ values < 30% of predicted. Analyses that treat the relationship between FEV₁ and plethysmographic TLC as a linear continuum may be prone to underestimating its magnitude.

Finally, the authors state that "TLC in COPD patients varies as a function of phenotype." Unfortunately, no citation is provided, and we are unaware of any good evidence for the relationship of TLC to COPD phenotype (emphysema vs chronic bronchitis) that is not potentially biased by the reported limitations in plethysmographic volume measurement.

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**Insufficient Evidence for Chest CT Scan in TB Outbreak Investigation**

**To the Editor:**

We read with interest the article by Lee et al.¹ in *CHEST* (May 2010) evaluating the role of chest CT scans in TB outbreak investigation. In a cohort of 87 patients with TB, 18 cases of active TB were diagnosed. Nine of these patients had normal chest radiographs but showed lesions suggestive of active TB on high-resolution CT (HRCT) scans. The authors conclude that inclusion of HRCT scanning in outbreak investigation may be helpful in differentiating active TB from latent TB infection more reliably. However, several aspects of this study are flawed and require further discussion.

First, a gold standard for the diagnosis of active TB on HRCT scans was not set. The presence of cavities, branching linear opacities, or multiple noncalcified nodules was used as defining active TB. These findings may indeed indicate active TB in the correct clinical setting but are by no means 100% specific.² In only three out of nine cases was active TB confirmed by culture examinations. In addition, both film readers were blinded to clinical information but not to the aims of the study, introducing observer bias for a diagnosis of active TB. This may also explain the exceptionally good interobserver agreement.

Second, a control group of patients without a suspicion of possible active TB (negative tuberculin skin test and y interferon test) was not included. The prevalence and significance of the chosen HRCT scan criteria in an asymptomatic population, with an equally large proportion of smokers, is unknown. The relatively high number of incidentally diagnosed pneumonias in the HRCT scan group (5/50) is an indication that diseases other than active TB are relatively frequent in this cohort.

Third, follow-up of all cases, including those with a normal chest radiograph initially, was performed using radiographs rather than HRCT scans. The treatment response of the positive cases on HRCT scans, which could have served as an additional measure to confirm the diagnosis, remains unknown.

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Last, of the nine additional cases diagnosed with HRCT scans, seven had clinical symptoms suggestive of a diagnosis of active TB and a positive γ interferon test result. The three culture-proven cases were all in this group. Even with a negative chest radiograph, it is debatable whether these patients would have been diagnosed and treated as latent infections in an outbreak investigation without the additional HRCT scan. Only two cases were asymptomatic patients with a positive γ interferon test. In neither of these was active TB proven, leading to the possibility that these may represent false-positive test results.

In conclusion, the previously documented higher accuracy of HRCT scans compared with chest radiographs in the detection of active pulmonary TB is again noted in this study. However, as a result of study design and the methodologic flaws described previously, the aim of the study to elucidate the role of HRCT scanning in outbreak investigation is not met. The conclusion that HRCT scans may differentiate active TB from latent TB infection in outbreak investigation is insufficiently supported by the data. As the authors mention in their discussion, the impact of additional HRCT scanning in TB outbreak investigation can only be assessed by randomized controlled trials with the incidence of active TB in each group of patients as the end point. In view of the high cost of CT scanning, particularly in a screening environment, such trials should include assessment of cost-effectiveness. Risks associated with increased exposure to radiation will also have to be taken into account. At present, there is insufficient evidence to justify the inclusion of HRCT scanning in TB outbreak investigation.

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Safety of Ipratropium Bromide

To the Editor:

I read the article by Ogale et al titled “Cardiovascular Events Associated With Ipratropium Bromide in COPD” in the recent issue of CHEST (January 2010). In the study, 93% of the cohorts who were exposed to anticholinergics were also using a short-acting β2-agonist. I think this may be the reason for the increased cardiovascular events in these patients. Metaanalysis done by Salpeter et al concluded that β2-agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events.

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Response

To the Editor:

As Dr Singh notes, short-acting β2-agonists (SABAs) have been associated with an increased risk of cardiovascular events (CVEs) in observational studies, as well as in a metaanalysis of clinical trials. He suggests the increased risk of CVEs associated with ipratropium bromide in our study could be attributed to SABAs because the two drugs are commonly used concomitantly. In our analysis, we adjusted for the standardized number of inhaled SABA canisters and any use of oral or nebulized β2-agonists and long-acting β2-agonists during the past year. After adjustment for SABA use, we observed an increased risk of CVEs [hazard ratio (HR) for four or fewer and more than four 30-day equivalents: 1.40 [95% CI, 1.30-1.51] and 1.23 [95% CI, 1.13-1.36], respectively] associated with ipratropium exposure within the past 6 months. To further address the issue raised by Dr Singh, we reanalyzed the dataset, excluding patients receiving ipratropium bromide and SABA concurrently. This analysis confirmed our prior conclusion that there is an increased risk of CVE with ipratropium exposure within the past 6 months (HR, 1.32; 95% CI, 1.07-1.64), independent of SABA use.