Spirometry: How Should We Order This Bedrock of Diagnosis and Management for Asthma and COPD?

Current guidelines for asthma and COPD begin with the need for a correct diagnosis, prompted by the history and physical exam and confirmed by spirometry demonstrating obstruction and assessing reversibility.[1–4] After determining that obstruction exists, additional tests are ordered based on their clinical utility, namely the likelihood that such tests will alter management or prognosis. As always, patient safety and rising healthcare costs are important concerns.

Because of its utility, specificity, and safety, post-bronchodilator spirometry is employed in the diagnosis of asthma[1,2] and to measure the acutely reversible component in COPD.[3,4] Curiously, neither the patient nor the physician is consistently accurate when estimating the degree of bronchoconstriction present,[1] and so the post-bronchodilator test has proved to be particularly useful in determining the severity of the disease and predicting the clinical response to bronchodilator therapy. The post-bronchodilator test is specific because a selective β_2 agonist is used, and relatively safe because it is delivered by inhalation.[5] By contrast, the methacholine challenge, which can be the next diagnostic step, is time consuming and requires close medical supervision, because a positive test requires one or more bronchodilator treatments to return the patient to a normal FEV_1.[6]

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In this issue of RESPIRATORY CARE, Hegewald et al[7] address an unanswered question about the bronchodilator response: is it necessary in the patient with normal spirometry? They reviewed the 1,394 normal spirometric tests (as defined by the American Thoracic Society/European Respiratory Society [ATS/ERS] Task Force on the Standardization of Lung Function Testing,[8] and using the National Health and Nutrition Examination Survey III reference equations and lower limits of normal[9]), performed between 2002 to 2008, with particular attention to the 43 tests that had a positive response to inhaled bronchodilators. This study was made possible because post-bronchodilator spirometry was routinely ordered. The population studied had 3 unique characteristics that limited variability as well as its generalizability: it was 93% white, it lived at altitude, and its smoking history (but not industrial exposure) was close to zero. They found that in their study population, 3.1% of individuals with normal spirometry had a significant bronchodilator response, but 0% of those with an $FEV_1 > 100\%$ of the value predicted from the reference equation. Patients with FEV_1 percentages and FEV_1/FVC ratios approaching the lower limits of normal were found to be the most likely to have a significant bronchodilator response. In addition, there was an increased likelihood for bronchodilator responsiveness if the patient was older than 65 years of age. The authors conclude that patients with normal spirometry that showed a pre-bronchodilator $FEV_1 > 100\%$ as predicted by their age, height, and race need not undergo post-bronchodilator spirometry.

When is the finding of a normal FEV_1 sufficient, and when is a post-bronchodilator test needed? The answers to these questions are guided by the clinical utility of the findings that might be obtained with further testing.

- No further pulmonary function testing need be done when spirometry is normal for the patient who presents with a presumptive diagnosis of COPD. This diagnosis generally requires that the post-bronchodilator FEV_1/FVC be < 0.7 (the Global Initiative for Chronic Obstructive Lung Disease [GOLD] rule, which unfortunately overdiagnoses the older patient[3,4]), and so a normal spirometry even before a bronchodilator precludes the diagnosis of COPD. One important caveat is that the appropriate use of the relevant National Health and Nutrition Examination Survey [NHANES] III reference equations and lower limit of normal[9] (as done in Hegewald[7]) avoids the underdiagnosing of younger patients and the overdiagnosing of older patients that is a characteristic of employing the GOLD cutoff criterion. In any case, additional testing of those with early COPD is probably not warranted, because pharmacologic interventions with such patients have not been shown to slow the progression of the disease.[3]
- Spirometry alone is again sufficient (when normal) for the patient monitored to assess the adequacy of management. If the prescribed treatments have already reversed the obstruction as measured by spirometry, an additional test is unlikely to yield information that will alter management.

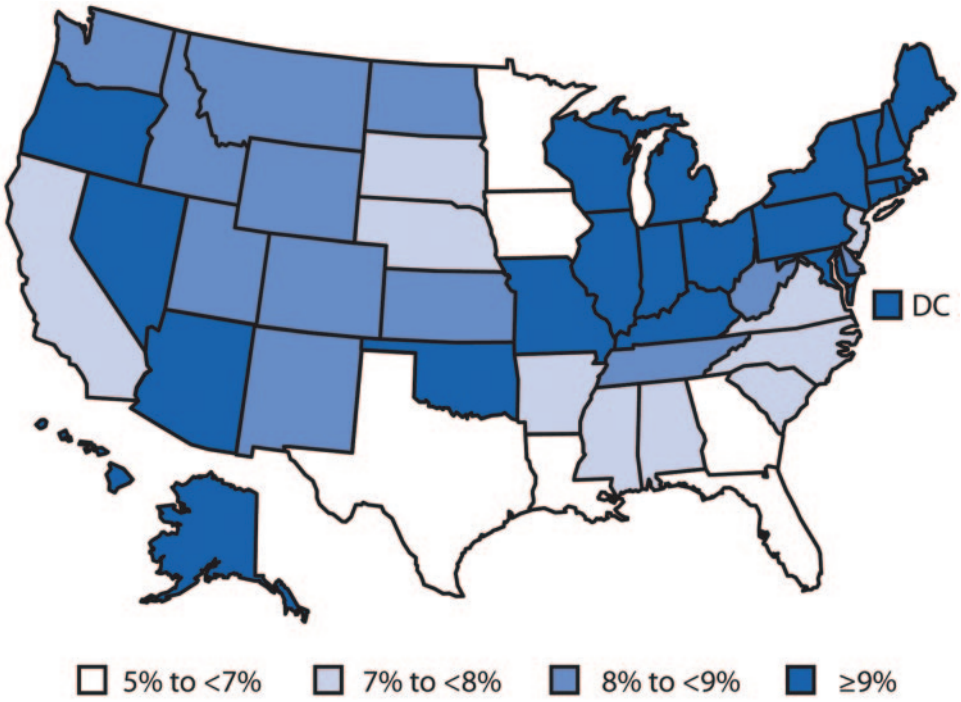

Fig. 1. Asthma prevalence among adults, 2009. Utah has a prevalence rate characteristic for the nation as a whole. DC = Washington, District of Columbia. (From Reference 10.)

What factors then should prompt a bronchodilator test, even in the face of normal spirometry?

- Has the patient presented with a family history, symptoms, and physical findings suggestive of asthma? A compelling narrative has always been cause for concern and a reason to aggressively pursue a diagnosis, and the study of Hegewald et al[7] reinforces this approach. The statistical analysis of Hankinson et al[9] defined normal according to intervals that included 95% of the subjects, and so 2.5% of their normal population fell below the lower limits of normal; indeed, this study by Hegewald et al[7] found 3.1% of their patients who were within the limits of normal for FEV_1 and FEV_1/FVC had a positive bronchodilator response. Hegewald et al[7] did not address whether these 3.1% were false negatives (the criteria of the FEV_1 and FEV_1/FVC falsely ruling out the diagnosis of reactive airway disease) or false positives (the positive bronchodilator response falsely supporting that diagnosis). However, the possibility of the patients' spirometry being a false negative result was strengthened by the finding that the individuals with low (but normal) FEV_1 percentages and FEV_1/FVC had higher rates of bronchodilator responses. Therefore the clinician is correct to seriously consider whether his patient with a normal spirometry (but a compelling story) has unrecognized obstruction. Under these circumstances a post-bronchodilator test would seem appropriate.
- Certainly, an individual who had previously shown bronchodilator responsiveness even though spirometry was within normal limits should be tested as needed.
- A patient with normal spirometry, but drawn from a population that has a high prevalence of asthma, would more likely merit a post-bronchodilator test than a patient from a COPD predominant population. While the study population of Hegewald et al[7] was drawn from a population with an average asthma prevalence (Utah: 8% to $< 9\%$ by the Behavioral Risk Factor Surveillance System telephone survey of 2009, Fig. 1),[10] COPD is much lower than average (age-standardized death rate for COPD, 2005–2007, Fig. 2).[11] In other states, such as Kentucky and Oklahoma, COPD is much more common, generally biasing the decision away from the need for a post-bronchodilator test, since its results would most likely not alter management of the patient.

To these considerations, Hegewald et al[7] add 2 more:

- Is the $FEV_1 > 100\%$ of the value predicted by the appropriate reference equation? Not one of the 429 normal spirometries with an $FEV_1 > 100\%$ of predicted had a positive post-bronchodilator test, making it imperative for the clinician to carefully reconsider a working diagnosis of asthma should the spirometry be normal and the FEV_1 be greater than 100% of predicted.

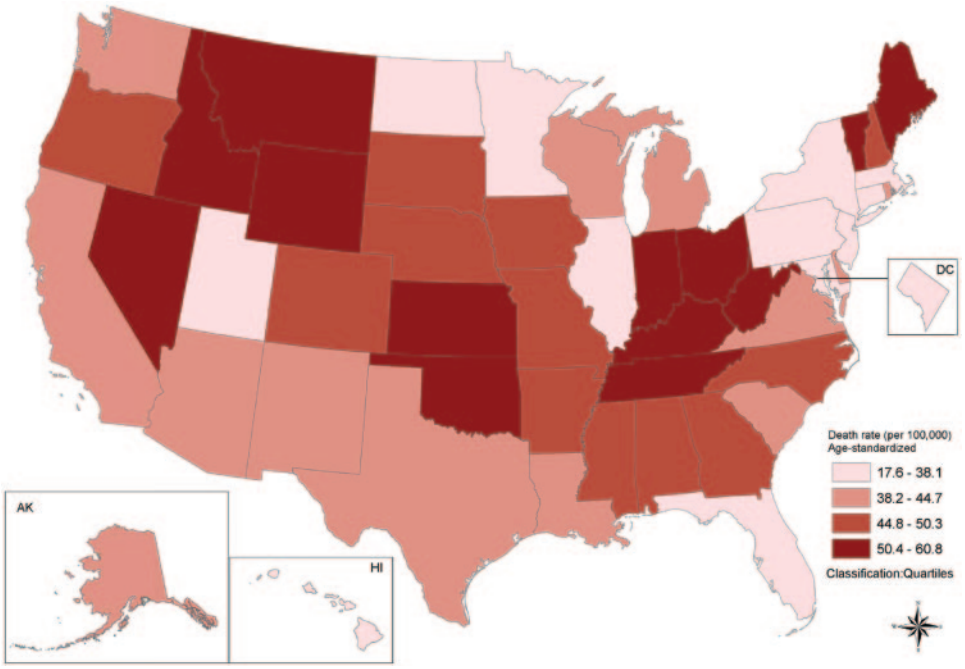

Fig. 2. Age-standardized death rate for COPD, 2005–2007.[11] Utah has one of the lowest rates of death by COPD in the nation. DC = Washington, District of Columbia. (From Reference 12.)

- Is the patient older than 65? If so, there is a greater than average chance for a positive post-bronchodilator response, just as there is a greater risk of death from asthma for white patients over 65, a risk that dramatically increases during the eighth decade of life[13] (Fig. 3), even though asthma prevalence changes little.[14] The confidence interval for FEV_1 is not a function of age,[15] depending only on the height of the patient.[9] Could it be that, for the older patient, the confidence interval for FEV_1 should increase with age?
- These findings are predicated on the use of appropriate reference equations and lower limits of normal,[9] and so it is of utmost importance that every pulmonary function laboratory employs the equation that is relevant to the individual patient being studied.

Is it time to re-think our protocols? Certainly, the routine ordering of bronchodilators with spirometry is of little use, and was wasteful for Hegewald et al[7] when the spirometry was normal, as it discovered no more people with reversible airway disease than randomly testing the population of Salt Lake City. On the one hand, simply omitting post-bronchodilator tests when spirometry is normal reduces costs (12% in our institution) and has no impact on the vast majority of subjects tested; but plans for cost containment require caution in order to not shift the economic burden onto those who had the false negative results, who will most likely require a 15-fold more expensive follow-up visit and spirometry at some point in the future.

One extreme protocol would be unacceptable: if no post-bronchodilator tests were performed on the 1,394 normal spirometries (and using our institution's allowable reimbursement schedule), the deferred costs of an additional office visit and spirometry for the 43 false negatives would alone be half the savings from doing no post-bronchodilator tests on the normal spirometries. Fortunately, all the false negatives were found in the normal spirometries where $FEV_1 \leq 100\%$ of the value predicted by the reference equation, allowing for cost containment without compromising care of the patient. Thus, the recommendation of Hegewald et al[7] is to forgo post-bronchodilator spirometry

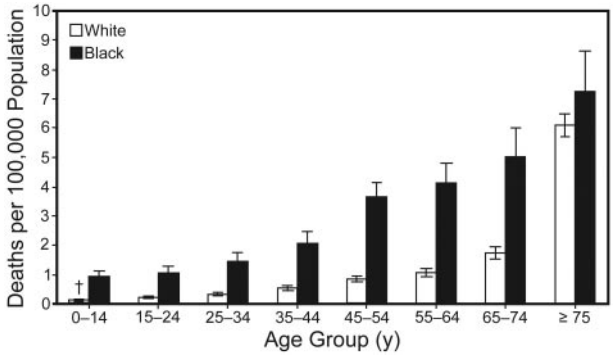

Fig. 3. Asthma death rate for 2007–2009. The death rate from asthma increases dramatically in the eighth decade for white patients, while the death rate for black asthmatic patients increases to the same point but at a more steady pace throughout their adult lives. (From Reference 13.)

on patients with *normal spirometry* and *FEV_1 > 100% predicted.*

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