Debunking myths in pulmonary function testing

Jeffrey M Haynes, RTT, RPFT, FAARC

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INTRODUCTION

The goal of evidence-based medicine is to move away from practices based on theory and replace them with practices based on robust scientific evidence. Unfortunately, many clinicians performing and interpreting pulmonary function tests dogmatically adhere to ideas based on theory despite evidence to the contrary. This paper will highlight examples of myths dressed up as science in the realm of pulmonary function testing. The goal of this paper is not just to inform but to also stimulate healthy debate and introspection about what we believe to be true and how these beliefs impact our practice and patient care.

MYTHS IN PULMONARY FUNCTION TESTING

Caffeine should be withheld prior to pulmonary function testing

As a member of the methylxanthine family, caffeine has been thought to possess bronchodilator properties. Because of this, the 1999 American Thoracic Society (ATS) guideline for methacholine and exercise testing recommended that caffeine-containing products be withheld on the day of testing [1]. While the 2005 ATS/European Respiratory Society guidelines for pulmonary function testing do not prohibit caffeine prior to testing [2], many laboratories continue to prohibit caffeine use prior to testing. It has been my experience that many patients are unhappy that they must withhold their morning coffee or tea prior to testing. Yurach et al [3] assessed the effect of caffeinated coffee on patients undergoing spirometry, methacholine challenge, and exhaled nitric oxide testing. The investigators found that a 16-ounce cup of coffee (~330 mg caffeine) had no effect on FEV_1, methacholine responsiveness, or mean exhaled nitric oxide (Table 1). Precluding patients from ingesting usual amounts of caffeine prior to pulmonary function testing is unwarranted.

Patients are usually the cause of poor quality data

Numerous studies have documented a high prevalence of poor-quality spirometry testing in both the pulmonary function laboratory and office settings [4, 5]. This has occurred at a time when spirometer accuracy and reliability appears to be much better than in the past [6]. It is therefore not surprising that most technologists can be expected to blame poor patient effort and cooperation for poor test quality [7]. However, the literature clearly indicates that most patients, even children [8] and the elderly [9], are capable of producing high-quality pulmonary function data. The key to higher quality pulmonary function data is technologist performance monitoring and feedback [7]. In the Lung Health Study, Enright et al [10] documented a reduction in spirometry test quality after initial technologist training, which improved with retraining, but could only be sustained with a program of on-going technologist performance monitoring. Borg et al [4] evaluated the effect of technologist monitoring and feedback in two clinical pulmonary function laboratories. Prior to the intervention, lab #1 and lab #2 had poor test acceptability and reproducibility rates, 61% and 59%, respectively. Lab #1 implemented a technologist performance monitoring and feedback program and lab #2 did not. In response to the intervention, lab #1's test quality rates rose to 92% while the quality of lab #2 remained poor at 65% (Figure 1). The unfortunate truth is that it is the technologist, and not the patient, who is usually the cause of poor quality testing. Pulmonary function laboratories should include technologist training and performance monitoring in their quality assurance programs.

TABLE 1

The effect of caffeinated coffee on pulmonary function

Parameter	Pre-coffee	Post-coffee*
FEV_1 (L)	3.31 (0.75)	3.36 (.74)*
PC_{20} (mg/mL)	1.36†	1.35*
FE_{NO} (ppb)	31.2 (19.6)	31.5 (20.4)

Note: Data are expressed as mean with standard deviation. FEV_1,= forced expiratory volume in the first second; PC_{20}, provocative concentration of methacholine causing a 20% decline in FEV_1;FE_{NO} = fraction of expired nitric oxide; ppb, parts per billion. Table produced with data from Yurach et al [3].

**p > 0.05.*

†Measured after decaffeinated coffee.

Only high-quality spirometry tests are meaningful

As stated above, high-quality test results should be the goal of every pulmonary function laboratory. However, there are always going to be some patients, albeit a minority, that will not be able to produce high-quality spirometry. When spirometry quality is not perfect, many technologists reject sub-optimal tests to avoid reporting spurious data. While the practice of discarding less-than-perfect spirometry data is well intentioned, it may frequently discard clinically useful data. Using an A-B-C-D-F scoring strategy, Hankinson et al [11] found that only quality scores of D or F affected test interpretation. While we must always strive for maximum quality, technologists and physicians should exercise caution when discarding data.

Technologists must scream at patients to obtain quality spirometry results

A typical lesson in spirometry testing includes stressing the importance of using a loud voice, to the point of yelling or screaming test instructions, to obtain maximum effort and quality data. This practice has no basis in science and in most situations is completely unnecessary. Yelling or screaming spirometry instructions can be frightening to children, annoying to teens, and less audible to those with hearing deficits. Demonstrating the maneuver to the patient prior to testing and using suggestive body language during testing is more effective than yelling or screaming instructions at the patient. Studies should be conducted to investigate the best way to communicate pulmonary function test instructions to patients.

$FEF_{25-75\%}$ aids in test interpretation

The forced expiratory flow over the middle half of the vital capacity ($FEF_{25-75\%}$) is believed by many to be representative of small airways function. A common interpretation of a "low $FEF_{25-75\%}$" is that the test results are "compatible with small airways disease." The problem with this interpretation is that $FEF_{25-75\%}$ has a very wide normal range

Pulmonary Function Laboratory, St Joseph Hospital, Nashua, NH
Correspondence: Jeffrey Haynes, Pulmonary Function Laboratory, St Joseph Hospital, 172 Kinsley St, Nashua, NH 03060, e-mail: jhaynes@sjhnh.org

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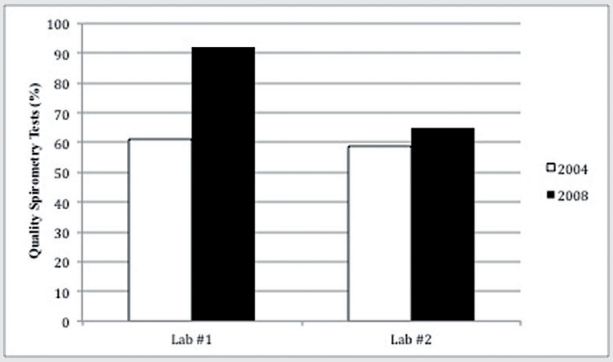
FIGURE 1

The percentage of quality spirometry tests from two clinical laboratories. Baseline data from 2004 is compared to 2008 after lab #1 instituted an on-going technologist performance monitoring and feedback program. Figure produced with data from Borg et al [4].



[12]. Indeed, after age 70 years, one can have an $FEF_{25-75\%}$ less than 50% of predicted and still be above the 5th percentile [13]. Quanjer et al [13] examined the impact of $FEF_{25-75\%}$ on test interpretation, they found the incidence of $FEF_{25-75\%}$ falling below the lower limit of normal as an isolated finding (i.e., normal FVC, FEV_1, and FEV_1/FVC) was only 2.75%. $FEF_{25-75\%}$ adds virtually nothing to the information provided by FVC, FEV_1, and FEV_1/FVC.

DLCO/VA can normalize an abnormal DLCO

For many clinicians, the interpretation of diffusing capacity (DLCO) is based on both DLCO and the DLCO to alveolar volume ratio (DLCO/VA). While it is undeniable that DLCO and lung volume are directly related, this relationship is both complicated and difficult to predict [14, 15]. A common mistake is to declare an abnormal DLCO normal if the DLCO/VA is within the normal range. This implies that the DLCO is low due exclusively to a lack of lung volume, not alveolar–capillary pathology. A recently published study by Pastre et al [16] shows that DLCO/VA can often be within the normal range even in patients with significant parenchymal lung disease. Therefore, DLCO/VA is not a reliable parameter for inverse modeling (i.e., predicting structure from function) [17].

80% of predicted is a reliable lower limit of normal

The interpretation of pulmonary function data requires knowledge of expected values in subjects without respiratory disease. To this end, reference or "predicted" equations are generated. The mean or median value for a pulmonary function value is referred to as the "predicted value." If the measured value is identical to the predicted value, the measured value is declared "100% of predicted." If the data are normally distributed, the predicted value will be found at the center of a symmetrical bell curve. In other words, there are an equal number of normal values above and below the predicted value. A long-standing and fundamentally flawed technique to define the lower limit of normal (LLN) of pulmonary function values is to multiply the predicted value by 0.80. The so-called "80% of predicted" rule declares any value below 80% as abnormal and vice versa. In 1979, Sobol and Sobol [18] commented that "nowhere else in medicine is such a naïve view taken of the limit of normal." The "80% rule" is statistically invalid for a number of reasons. Firstly, the normal ranges for different pulmonary function values are not identical. In addition, the normal variance around any value is affected by age, race, and gender [19]. As previously mentioned, after age 70 years, an $FEF_{25-75\%}$ value less than 50% of predicted can still be normal [13]. Quanjer et al [20] found that using the "80% of predicted" rule and 0.70 as the LLN for FEV_1/FVC misclassified >20% of patients. Wesolowski et al [21] documented that 14% of surgical lung cancer patients had pulmonary function values which were both <80% of predicted and above the LLN. This difference proved to be clinically important because having lung function below the LLN was a better predictor for perioperative complications than lung function <80% predicted but also ≥ LLN. Pulmonary function data should not be interpreted using 80% of predicted as the LLN (Figure 2, [22]).

A positive methacholine challenge confirms asthma

Methacholine challenge tests (MCT) are performed to test for the presence or absence of airway hyper-responsiveness (AHR) [23]. AHR is clearly a feature of asthma; however, AHR is not exclusive to asthma. For example, Leone et al [24] found that 46% of patients with non-allergic rhinitis with eosinophilia syndrome and no respiratory symptoms demonstrated AHR to methacholine. AHR is also a feature of COPD [25], sarcoidosis [26], and allergic rhinitis [27]. In addition, some subjects with no signs or symptoms of asthma demonstrate AHR to methacholine (asymptomatic AHR) [28, 29]. In patients with an intermediate pre-test probability of asthma, AHR in response to MCT may significantly increase the post-test probability of asthma. When the post-test probability of asthma is higher than the pre-test probability of asthma, a working diagnosis can be made. However, it is prudent to document an improvement in symptoms and lung function in response to therapy before making a working diagnosis of asthma official.

A negative methacholine challenge excludes asthma

As mentioned above, MCTs are performed to test for the presence or absence of AHR [23]. A lack of demonstrable AHR in response to MCT may significantly decrease the post-test probability of asthma; however, the sensitivity of MCT is not 100%. Indeed, Anderson et al [30] found that 45% of children with a positive exercise challenge had a negative methacholine challenge. In a study of elite athletes, the sensitivity of MCT to identify a positive response to eucapnic voluntary hyperventilation was only 36% [31]. The failure of MCT to identify asthma with

FIGURE 2

The percent of predicted lower limit of normal as a function of age in males and females. The red horizontal dashed line represents 80% of predicted. LLN, lower limit of normal; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity. From Quanjer et al [22] (open access material under CC-BY-NC license).

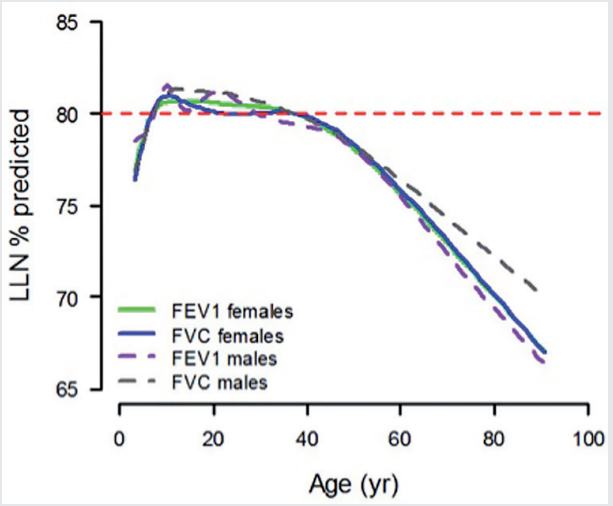
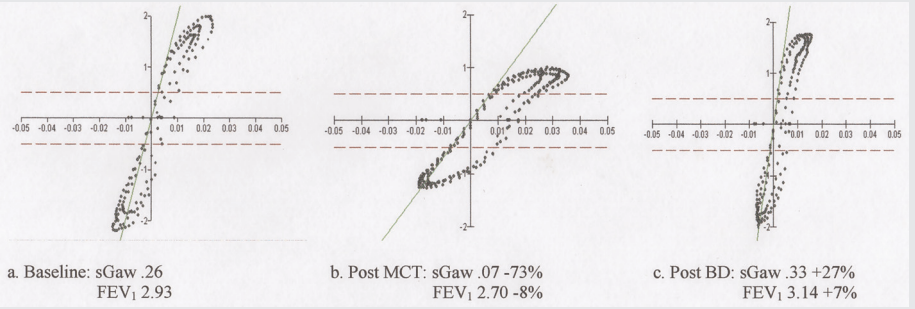


FIGURE 3

sGaw and FEV_1 in a symptomatic patient during a MCT. (A) Baseline testing before methcholine challenge test (MCT). (B) Post MCT. (C) Post BD administration. sGaw, specific airway conductance; FEV_1. forced expiratory volume in 1 second; MCT, methacholine challenge test; BD, bronchodilator). From Haynes [35] with permission.



perfect sensitivity is multi-factorial including both physiologic and technological considerations.

From a physiologic standpoint, phenotypic differences among asthmatics may affect the response to MCT [32]. In addition, the response to methacholine may be affected by seasonal variations in AHR. For example, Sposato et al [33] found a greater prevalence of AHR to methacholine in the spring and fall than during the summer months. Fruchter and Yigla [34] also found a higher incidence of AHR to methacholine in winter and spring when compared to summer. It is probably not uncommon for a patient to experience respiratory symptoms during the height of spring pollen season but not have their MCT scheduled until months later, after their allergen exposure has waned.

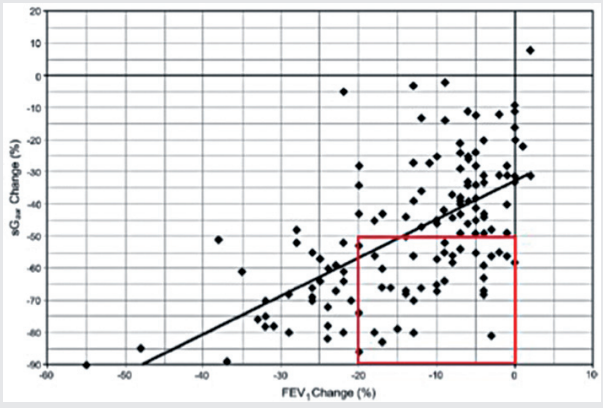
There are also technologic and methodological factors that can affect the results of a MCT. Methacholine dose, nebulizer type, inhalation method (e.g., dosimeter versus tidal breathing), and the threshold for a "positive test" can all affect MCT interpretation [1].

The impact of the bronchodilatory and bronchoprotective effect of deep inhalation on MCT has received a lot of attention. Cockcroft and Davis [35] have shown that using the full inhalation dosimeter method can significantly reduce the response to MCT and may result in false negative tests in patients with mild AHR.

In addition, relying solely on FEV_1 as a MCT outcome measure may reduce MCT sensitivity for AHR. An example of a patient with respiratory symptoms, markedly reduced specific conductance (sGaw), yet little to no change in FEV_1 during MCT is shown in Figure 3 [36]. Khalid et al [37] evaluated sGaw and FEV_1 in 138 patients undergoing a MCT. The researchers found that a 51–52% reduction in sGaw was a more appropriate cut-off point for a positive MCT than the 45% reduction recommended by the ATS [1]. A remarkable finding was that 32 patients with an FEV_1 decline <20% had a reduction in sGaw >50% (Figure 4). In a similar study, Parker and McCool [38] measured FEV_1 and sGaw following MCT in 248 consecutive patients with asthma-like symptoms. Forty patients showed a response to methacholine as assessed by sGaw (≥ 40% reduction) without a significant decline in FEV_1 (<20%). A negative MCT reduces the post-test probability of asthma; however, clinicians should be mindful that a negative MCT cannot rule out asthma with 100% certainty.

FIGURE 4

Change in sGaw versus FEV_1 in patients undergoing MCT. The red square includes subjects with a >50% reduction in sGaw with a <20% reduction in FEV_1. The black line is the linear regression line. sGaw, specific airway conductance; FEV_1, forced expiratory volume in 1 second; MCT, methacholine challenge test. From Khalid et al [36] with permission.



A negative exercise challenge test excludes exercise-induced bronchospasm

Exercise challenge tests are commonly performed to identify or exclude exercise-induced bronchospasm as the source of exercise limitation and symptomatology [1, 39]. An obvious limitation of exercise challenge tests is that they are not performed under the same circumstances as those from where the patient's symptoms originate. This is perhaps no more true than patients involved in cold-weather athletics. Rundell et al [40] performed field exercise challenge testing in elite cold-weather athletes; 78% of athletes with a positive field exercise challenge test had a negative exercise challenge test in a clinical laboratory. Differences between field and laboratory testing may be due to differences in exercise pattern and intensity as well as environmental factors such as ambient humidity and air quality. Anderson et al [41] performed two exercise challenge tests within four days in 373 subjects with asthma-like symptoms associated with exercise. While most subjects had either two positive or two negative tests, 23.9% of subjects had conflicting results (i.e., one positive, one negative). Exercise intensity could not explain the differences in test outcome. For these reasons, a single negative exercise challenge test cannot by itself exclude the possibility of exercise-induced bronchoconstriction.

Normal spirometry excludes emphysema

An irreversible obstructive spirometry test in a patient with COPD risk factors defines the disease [42]. However, over the past several years it has become known that COPD has many phenotypes [43]. Some of these phenotypes refute the paradigm that normal spirometry precludes

COPD pathology. For example, the COPDGene investigators found that 24% of current or former smokers with normal spirometry and a GOLD 0 classification had computed tomography evidence of emphysema [43]. Another poorly appreciated syndrome associated with cigarette smoking is combined pulmonary fibrosis emphysema (CPFE). Patients with CPFE have radiologic evidence of upper lobe emphysema and lower lobe fibrosis [44]. Patients with CPFE typically have a low diffusing capacity, elevated alveolar–arterial oxygen gradient, but normal spirometry and lung volumes [45]. Relying solely on spirometry to diagnose or exclude disease in symptomatic smokers can be expected to misdiagnose many patients with emphysema and CPFE.

Delta FEV1 effectively assesses bronchodilator response in COPD

As mentioned above, spirometric indices such as FEV_1 are widely relied upon to make a diagnosis of COPD. As a consequence, many clinicians use ΔFEV_1 to assess bronchodilator response/benefit in COPD patients. While patients with COPD can demonstrate significant increases in FEV_1 after bronchodilator, many do not. A not so uncommon yet mistaken conclusion is that an insignificant ΔFEV_1 indicates a lack of therapeutic efficacy. However, it is important to keep in mind that COPD patients seek medical care for dyspnea, not a recalcitrant FEV_1. Bronchodilators reduce dyspnea on exertion by reducing the rate of dynamic hyperinflation [46], which may not be accompanied by an arbitrarily agreed upon "significant" ΔFEV_1. O'Donnell et al [47] studied acute bronchodilator response in COPD patients who did not show improvement in FEV_1. These patients showed significant reduction in hyperinflation (i.e., increased inspiratory capacity, reduced residual volume) despite no change in FEV_1. Similar findings were recently shown by McCartney et al [48]. In their study, many COPD patients showed marked reduction in residual volume after bronchodilator despite little change in FEV_1. Judging bronchodilator response in COPD patients solely on ΔFEV_1 may lead to an under-appreciation of clinically important improvements in lung function, exercise capacity, and quality-of-life.

SUMMARY

Evidence-based medicine has revolutionized both diagnostics and therapeutics. However, the age of evidence-based medicine has not made pulmonary function laboratories immune from policies, procedures, and mistaken beliefs borne of myth and unproven theory. Indeed, pulmonary function guidelines contain recommendations based on both scientific data and unproven expert opinions. Pulmonary function technologists should be on the forefront of incorporating evidence-based practices in pulmonary function laboratories.

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