Redefining Spirometry Hesitating Start Criteria Based on the Ratio of Extrapolated Volume to Timed FEVs

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Background: The primary purpose of this study was to investigate alternative hesitating start criteria for spirometry maneuvers that do not achieve an acceptable plateau. The current hesitating start criterion that has been in use for 30 years is based on clinical opinion from expert users; it was not established based on information from peer-reviewed scientific studies.

Methods: A total of 1,719 workers met the eligibility criteria for this study and contributed 24,945 trials. The fitted lines obtained from linear regressions of each dependent variable, volume of air calculated at time zero using the back extrapolation method (extrapolated volume [EV])/FEV₁, EV/FEV in 3 s (FEV₃), and EV/FEV in 6 s (FEV₆) on EV/FVC were determined. The 95th percentile of the prediction interval of each dependent variable corresponding to EV/FVC = 5% was calculated.

Results: The values for EV/FEV₁, EV/FEV₃, and EV/FEV₆ corresponding to the 5% EV/FVC value were determined to be 6.62%, 5.59%, and 5.25%, respectively.

Conclusions: A new hesitating start criterion using EV/FEV₆ of 5.25% is recommended for tracings that do not achieve a plateau or when an FEV₆ is performed. An EV/FEV₃ of 5.59% could be incorporated into spirometry software as an early warning signal that could help operators identify trials with potential hesitating starts.

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Abbreviations: ATS = American Thoracic Society; ERS = European Respiratory Society; EV = extrapolated volume; FET = forced expiratory time; FEV₃ = FEV in 3 s; FEV₆ = FEV in 6 s; FWMMP = Fernald Worker Medical Monitoring Program; PFT = pulmonary function test

Pulmonary function tests (PFTs) are used routinely as screening tools to measure lung function, with spirometry most commonly performed. PFT standards have been established by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) to make administration and interpretation of spirometry uniform.^{1–3} Test acceptability criteria

and the definition of a hesitating start were adopted in 1979 by experts in the medical community.⁴ However, the hesitating start criterion was not established based on peer-reviewed scientific studies. The primary purpose of the current study was to investigate alternative hesitating start criteria for shorter forced expiratory times (FETs) with a high degree of correlation to the currently accepted method.

Measurement of FEVs on volume-time tracings uses the back extrapolation technique to identify time zero. PFT trials with excessive hesitating starts are not representative of forced expiratory maneuvers, and they are not usable for reporting forced expiratory measurements of lung function.

A spirometric trial with an excessive hesitating start is defined as having a ratio of volume of air calculated at time zero using the back extrapolation method (extrapolated volume [EV]) to FVC $\geq$ 5%, or an EV $>$ 150 mL, if the FVC is $\leq$ 3 L.² Achieving an

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acceptable FVC requires a subject to reach a plateau on volume-time tracings. A plateau is indicated by a change in volume of $< 25\text{ mL}$ for $\geq 1\text{ s}$.² Some subjects are unable to achieve an acceptable plateau when conducting a forced expiratory maneuver for a variety of reasons, including medical conditions. Failure to achieve an acceptable plateau alters the calculated ratio of EV to FVC, which may change the decision as to whether a maneuver has an acceptable start.

FEV in 6 s (FEV₆) has been shown to be an acceptable surrogate of FVC.⁵⁻⁸ Exhalation for 6 s is also better tolerated than complete exhalation to FVC. Tracings without a plateau underestimate FVC, elevating the calculated EV/FVC ratio and increasing the likelihood of rejection due to a hesitating start. Therefore, when a plateau is not reached, the calculation of a hesitating start based on shorter FET, rather than FVC, would appear to be more appropriate, to reduce the chance of falsely rejecting the trial. Many patients and spirometry technicians could benefit from the development of criteria that define a hesitating start based on EV/FEV₆, rather than one based on EV/FVC.

MATERIALS AND METHODS

This study was a retrospective cohort study of subjects included in the Fernald II Settlement, who participated in the Fernald Worker Medical Monitoring Program (FWMMP)⁹ and who had at least one PFT session. All data were deidentified. Subjects represented a worker and former-worker population at a uranium processing plant in Fernald, Ohio. Workers were followed to monitor for potential health effects from occupational exposure to uranium and radiation. A total of 1,719 Fernald workers met the eligibility criteria for this study and contributed 24,945 trials.

Spirometry measurements used for this study were collected between January 2000 and October 2008. Subjects were tested approximately every other year and completed multiple trials within each test session (all spirometry trials completed by one subject were on the same day). The spirometry tests were administered by experienced pulmonary function specialists who had completed a National Institute for Occupational Safety and Health-approved training course. Computerized data were acquired according to ATS/ERS standards using OMI spirometry software (Houston, Texas) connected to an 8-L SensorMedics 922 volume spirometer (SensorMedics Inc; Yorba Linda, California). Volume-time and flow-volume tracings were collected, which allowed calculation of FVC, FEV₁, FEV in 3 s (FEV₃), FEV₆, EV, and FET. Time zero was calculated using back-extrapolation.

Inclusion criteria for regression analyses were (1) spirometry trials (forced expiratory maneuver by a subject) without invalid or missing forced expiratory measurements, (2) spirometry trials meeting ATS/ERS acceptability criteria, and (3) acceptable spirometry trials with EV/FVC $< 5\%$. Using these criteria, 13,025 trials from 1,501 participants were included in the analyses. A total of 11,920 trials did not meet regression inclusion criteria, and the majority of these (11,397 trials) were excluded for failure to meet acceptability criteria. The most common exclusion was failure to reach a plateau, as shown in Table 1. Four hundred eighteen trials were excluded because of invalid/missing information and practice testing. These trials were performed for teaching or maintenance,

or contained missing/corrupted pulmonary function measurements. One hundred five acceptable trials with EV $< 150\text{ mL}$ were excluded because they had EV/FVC $\geq 5\%$. The subjects removed from analysis were slightly older (64 vs 70 years), with slightly lower lung function values.

For the sensitivity and specificity analysis of the EV/FEV₆ value, it was necessary to modify the inclusion criteria. The inclusion criteria for the sensitivity and specificity analyses were the same as those in the regression analyses, except that trials rejected from the regression analysis solely for having an EV/FVC $\geq 5\%$ (an excessive hesitating start) were included. The institutional review board at the University of Cincinnati and the Fernald Worker's Advisory Group approved the study.

Statistical Analysis

Exploratory analyses were performed to assess worker demographics (gender, race, age at test, BMI, smoking status), test characteristics (maximum number of trials per subject, number of subjects at each test session, number of trials per test session), and distributions of spirometric variables (FVC, FEV₁, FEV₃, FEV₆, EV, EV/FVC, and EV/FEV₁). Graphic displays supported the assumption of normality of spirometric variables. The range and magnitude of Pearson correlations between spirometric measures on the same subject within the same session were calculated in preparation for the regression analyses. Three separate linear regression models that included data from all acceptable trials of 1,501 subjects (ie, EV/FVC $< 5\%$) were analyzed to estimate the (statistical) predicted values of each dependent variable (EV/FEV₁, EV/FEV₃, and EV/FEV₆) corresponding to an EV/FVC of approximately 5%. Because multiple acceptable trials for the same subject were included in the analyses, repeated-measures analyses were performed. The average correlation between pairs of spirometric measures on the same subject was constant for differing intervals between tests; therefore, an exchangeable correlation structure was assumed. The 95th percentile of the prediction interval of each dependent variable corresponding to EV/FVC = 5% was calculated and was used to identify new hesitating start cutoff values for EV/FEV₁, EV/FEV₃, and EV/FEV₆. The newly calculated EV/FEV₆ cutoff value was applied to trials rejected solely for not reaching a plateau and also to trials rejected solely for having a hesitating start as determined by OMI software. Secondary analyses were performed to investigate the effect of spirometry pattern on values of EV/FEV₆ corresponding to values of EV/FVC approximating 5% for subjects classified into normal, obstructive, restrictive, and mixed spirometry patterns based on National Health and Nutrition Examination Study III reference equations.¹⁰ Again, the 95th percentile of the prediction interval of EV/FEV₆ corresponding to EV/FVC = 5% was selected as the cutoff value. An additional analysis was performed in which the sensitivity and specificity of the new cutoff value at 6 s was calculated using the currently accepted hesitating start cutoff value based on EV/FVC as the gold standard. All data were analyzed using SAS statistical software, version 9.1 (SAS Institute; Cary, North Carolina).

RESULTS

Acceptable trials from 1,501 participants (13,025 trials) were analyzed. A summary of the slopes of the regression of EV/FEV₁, EV/FEV₃, and EV/FEV₆ on EV/FVC is provided in Table 2. Slope coefficients reflect changes in the dependent variables corresponding to a one-unit change in EV/FVC (%), which was the independent variable in each analysis.

Table 1—Number of Unacceptable Spirometry Trials by ATS/ERS Acceptability Criteria

Rank Order (Based on Rejected Trials)	ATS/ERS Criteria Not Met	Rejected Trials, No. (%)	Unique Subjects, No.
1	No plateau	6,025 (53)	1,156
2	Unacceptable peak flow	1,193 (10)	556
3	No plateau and FET < 6 s	794 (7.0)	351
4	No plateau and unacceptable peak flow	579 (5.1)	348
5	EV/FVC $\geq$ 5%, or 150 mL, whichever was greater	513 (4.5)	270
6	No plateau, FET < 6 s, and unacceptable peak flow	452 (4.0)	349
7	Large EV and unacceptable peak flow	299 (2.6)	200
8	No plateau and large EV	299 (2.6)	187
9	No plateau, large EV, FET < 6 s, and unacceptable peak flow	209 (1.8)	167
10	FET < 6 s	173 (1.5)	79
11	All other combinations ^a	861 (7.6)	709
Total		11,397 ^b (99.7 ^c)	4,293 ^d

Rejected trials are specific for criteria listed in same row. A plateau was defined as a change in volume < 25 mL during the last second of the forced expiratory maneuver. An unacceptable peak flow was typically defined as a peak flow for any given trial that was not within 20% of the highest acceptable peak flow. An exception is often given when the highest peak flow < 6 L/s. In all cases, the shape of the flow-volume tracing was used to determine if an acceptable peak flow was achieved. ATS/ERS = American Thoracic Society/European Respiratory Society; EV = extrapolated volume; FET = forced expiratory time.

^aData available on request.

^b11,397 spirometry trials were rejected because of ATS/ERS acceptability criteria, and 3,367 of these trials did not meet more than one ATS/ERS acceptability criterion.

^c< 100% due to rounding.

^dSubjects contributed trials in multiple categories.

Table 1 shows the number of unacceptable spirometry trials by ATS/ERS acceptability criteria. Overall, 10% of rejected trials (1,156 of 11,397) had a hesitating start. Table 3 shows the demographic and selected clinical characteristics of the cohort. From the regression analyses, the hesitating start cutoff values for EV/FEV₁, EV/FEV₃, and EV/FEV₆ were 6.62%, 5.59%, and 5.25%, respectively, as determined from the 95th percentile of the prediction intervals corresponding to EV/FVC = 5%. Figure 1 shows a volume-time tracing with the cutoff values defining a hesitating start at 1, 3, and 6 s of exhalation.

To evaluate the newly developed hesitating start criteria, the data from 13,025 ATS/ERS acceptable, and therefore plateau-adequate, tracings were truncated at 6 s to simulate maneuvers with early termination (ie, no plateau). Truncating the maneuvers at 6 s for the analysis caused the “false” rejection of 162 trials (1.2%) when the current EV/FVC-based cutoff value of 5% was applied to these truncated trials. In reality, all these maneuvers had demonstrated acceptable starts when the expiration was permitted to reach a plateau. Applying the newly developed hesitating start criteria based on EV/FEV₆ of 5.25% to the trials truncated at 6 s resulted in a modest increase in the number of acceptable trials (162–37 = 125, 0.96%), compared with applying the currently accepted hesitating start criteria based on EV/FVC of 5%.

Acceptable trials (n = 13,025) were also truncated at 3 s to evaluate the usefulness of a potential early

warning system for identifying a hesitating start. The EV/FEV₃ criterion established at 3 s was 5.59%.

Trials rejected solely for not achieving a plateau (n = 6,025) were truncated at 6 s, and the EV/FEV₆ cutoff value of 5.25% was applied. This resulted in 28 trials (0.46%) being classified as having acceptable starts, compared with 48 trials (0.80%) when the conventional cutoff value of 5% was applied.

The spirometry pattern subgroup regression analyses derived from the 13,025 acceptable trials produced EV/FEV₆ hesitating start cutoff values of 5.24% for the normal (neither obstructive nor restrictive) subgroup, 5.66% for the obstructive subgroup, 5.25% for the restrictive subgroup, and 5.63% for the mixed (obstructive and restrictive) subgroup. Table 4 shows the number of trials rejected after applying these subgroup-specific hesitating start cutoff values to acceptable trials truncated to 6 s that were categorized by spirometry pattern. The conventional EV/FVC cutoff value of 5%, the newly calculated overall

Table 2—Slopes of Regressions

Dependent Variable ^a	Slope ^b
EV/FEV ₁	1.31
EV/FEV ₃	1.11
EV/FEV ₆	1.05

FEV₃ = FEV in 3 s; FEV₆ = FEV in 6 s. See Table 1 for expansion of other abbreviations.

^aP < .05 testing the goodness of fit of each model by the Kolmogorov-Smirnov test statistic.

^bP < .01 testing the slope coefficient of EV/FVC = 0 in each model.

Table 3—Demographic and Selected Spirometric Characteristics of Subjects Contributing Acceptable Trials

Characteristics	Values (n = 1,501)
Gender	
Male	1,172 (78)
Race	
White	1,411 (94)
Black	81 (5.4)
Other	9 (0.61)
Age at test, y	63 ± 11
BMI	29 ± 5
FEV ₁ /FVC%	74.5 ± 7
Smoking status ^a	
Former	740 (49)
Never	613 (41)
Current	146 (10)

Data are presented as No. (%) or mean ± SD.

^aThe total number of subjects differs because of missing data.

(not subgroup-specific) EV/FEV₆ cutoff value of 5.25%, and the EV/FEV₃ cutoff value of 5.59% were also applied to each subgroup. None of the tracings truncated in the obstructive and mixed subgroups were identified as having a hesitating start when the newly developed subgroup-specific criteria were applied. This finding conforms to expectation because the obstructive and mixed subgroup-specific cutoff values are higher than the currently accepted cutoff value (5.66% and 5.63% vs 5%).

The sensitivity and specificity analysis of the overall 5.25% EV/FEV₆ cutoff value included the 13,025 acceptable trials plus 513 additional excessive hesitating start trials that had been rejected from the regression analysis for the sole reason that their EV/FVC value was $\geq 5\%$. The gold-standard comparison used was the current 5% EV/FVC criterion. The results of this evaluation using the new 5.25% EV/FEV₆ criterion were a sensitivity of 99.7% and a specificity of 94.9%. The new EV/FEV₆ cutoff was applied to the 513 trials rejected solely for having a hesitating start, as determined by the current hesitating start criteria, and this resulted in the rejection of 413 (80%) of the trials.

DISCUSSION

This study identified hesitating start criteria for spirometry trials that do not achieve a plateau and therefore do not have a true FVC. These criteria are especially useful in clinical settings where tracings are stopped early for legitimate medical reasons or when conducting the FEV₆ maneuver. This may be of value because many computerized spirometry systems report the largest exhaled volume as the FVC, even when forced expiration is terminated early. Using an

FIGURE 1. Volume-time tracing showing cutoff values defining a hesitating start at 1, 3, and 6 s of exhalation for 1,501 workers (n = 13,025 trials). Values reported for EV/FEV₁, EV/FEV₃, and EV/FEV₆ are the 95th percentile of the prediction interval corresponding to EV/FVC = 5%. EV = extrapolated volume; FEV₃ = FEV in 3 s; FEV₆ = FEV in 6 s.

FVC from an early-terminated maneuver may influence whether an acceptable start was achieved.

Our study population consisted of older workers and former workers with a mean age of 63 years. The most common reason for excluding trials from the database used to derive our new hesitating start criterion was the lack of a plateau, despite vigorous coaching and lengthy FETs. Currently, a hesitating start is determined by the ratio of EV to the recorded FVC (the total exhaled volume of the trial), whether or not a plateau is achieved. Therefore, failure to achieve a plateau reduces the recorded FVC and falsely elevates the calculated EV/FVC ratio. In trials with low FVC, a hesitating start may also be determined based on the absolute size of the EV (150 mL). We propose no change to this part of the hesitating start criterion and recommend its continued use when applying our new criterion for maneuvers that do not achieve a plateau.

In our study, when the new EV/FEV₆ criterion was applied to acceptable maneuvers truncated to shorter expiratory times for purposes of this study, a small increase in the number of acceptable trials was found compared with the current hesitating start cutoff. A similar increase in the number of acceptable trials was found when the new EV/FEV₆ cutoff was applied to trials that simply lacked an acceptable plateau. In both cases, the increase in the number of acceptable trials (about 1%) was rather small. However, in the absence of our recommendation, programs that routinely conduct FEV₆ maneuvers may logically conclude that use of the EV/FVC cutoff of 5% is inappropriate for the reasons discussed. Lacking a specific recommendation, they may use another, unsubstantiated value to define an excessive hesitating start. Our data show

Table 4—Number of Trials Rejected After Applying Hesitating Start Cutoff Values for EV/FEV₆ and EV/FEV₃ to Acceptable Trials by Category of Spirometry Pattern¹⁰

Group	Trials, No. (%)	6-s Truncated Trials Rejected Using Cutoff Value EV/FVC = 5%, No.	6-s Truncated Trials Rejected Using Cutoff Value EV/FEV ₆ = 5.25%, No.	3-s Truncated Trials Rejected Using Cutoff Value EV/FEV ₃ = 5.59%, No.	6-s Truncated Trials Rejected Using Subgroup-Specific Cutoff Value, ^a No.
Normal ^b	9,848 (76)	120	21	31	24
Obstructive ^{c,d}	1,053 (8)	10	7	9	0
Restrictive ^e	1,810 (14)	28	6	11	6
Mixed ^f	314 (2)	4	3	4	0
Total	13,025 (100)	162	37	55	30

FEV_{25-75%} = mean forced expiratory flow from 25% to 75% of FVC; LLN = lower limit of normal. See Table 2 for expansion of the other abbreviations.

^aSubgroup-specific cutoff values were 5.24% (normal), 5.66% (obstructive), 5.25% (restrictive), and 5.63% (mixed).

^bFEV₁/FVC% > LLN and FVC > LLN and FEV_{25-75%} > LLN.

^cFEV₁/FVC% < LLN and FVC > LLN.

^dThe low frequency of obstructive trials occurred because many trials with an obstructive pattern did not reach a plateau and were excluded from the analysis.

^eFEV₁/FVC% > LLN and FVC < LLN.

^fAll others.

that the calculation of EV/FEV₆ is a good replacement for EV/FVC for determining the excessive hesitating starts for spirometry trials with at least 6 s of exhalation but that do not reach a plateau.

Another application is that an EV/FEV₃ cutoff of 5.59% could be incorporated into spirometry software as an early warning tool to help identify potential hesitating starts. For example, an audible and/or visual warning could alarm at 3 s if a potential hesitating start was detected using the new EV/FEV₃ values reported in this study. This could help testing technicians who suspect an unacceptable start but desire objective data to support their decision. Stopping a maneuver earlier could reduce stress for some subjects, reinforce the technician's role in administration of the test, and ultimately improve test quality. Ten percent of rejected trials in our study had a hesitating start, and further patient effort could have been prevented by use of the early warning tool. Regardless of the criterion used to terminate a maneuver, testing technicians should be trained to recognize that clinically useful data can be obtained from marginal spirometry maneuvers. Consequently, the testing technician should carefully evaluate whether it would be appropriate to stop a maneuver based on EV/FEV₃. Another use could be for "office" spirometers that do not provide real-time tracings. Operators of this type of equipment may benefit from an early warning signal.

In the spirometry pattern subgroup analysis (restrictive, obstructive, and so forth), the subgroup-specific hesitating start criteria based on FEV₆ ranged from 5.24% to 5.66%. In a general population, a value of 5.25% is recommended. However, for individuals with known airway obstruction, our data suggest that a value of 5.66% may be more appropriate. Nevertheless, expanding the criterion to 5.66% for those with

known airway obstruction should be done cautiously. Additional research is needed to find the optimal hesitating start criterion in individuals with airway obstruction, because this value is highly correlated with FET. In addition, in the presence of air trapping, increasing the severity of airway obstruction does not always correlate with an increasing FET. Until additional information becomes available, the more conservative value of 5.25% is recommended.

With respect to our study population, the number of participants, number of trials, experience of the testing technicians, and use of testing procedures that adhered to ATS/ERS guidelines are strengths of the study. Despite the experience of our testing technicians and long FETs, many of our subjects were unable to reach a plateau. This may have been because experienced technicians are better trained to recognize medical conditions that preclude obtaining a plateau for safety reasons. In addition, our study population was older than most. Both circumstances likely contributed to the large number of trials that did not reach a plateau. Therefore, although many tracings were excluded from the primary database used for analysis, 13,025 tracings with acceptable plateaus remained. These 13,025 tracings were then available for truncation to shorter expiratory times.

A limitation is that the study population was not representative of the general population because of older age, predominance of male gender, white race, and occupational exposures to uranium and radiation. Although the study population was not representative of the general population, it was representative of the type of subjects (eg, older) who may need to stop forced expiratory maneuvers at 6 s. The study population was also representative of the type of population that participates in spirometry testing for occupational exposures.

Our study does not show whether the new hesitating start criteria were better or worse than the currently accepted 5% EV/FVC value. However, it does show that the new values were highly correlated with the current EV/FCV value of 5% and that the new hesitating start criterion could be used as a highly sensitive and specific surrogate for determining excessive hesitating when a plateau is not achieved. Use of the currently accepted hesitating start criteria is still recommended for trials that achieve a plateau.

CONCLUSIONS

The use of hesitating start criteria based on EV/FEV₆ would have the greatest impact on individuals unable to achieve a plateau while performing spirometry trials. Slightly more trials would be classified as having an acceptable start of test when a plateau is not achieved, compared with the currently accepted method. The potential benefit would be fewer prolonged forced expiratory maneuvers, thus decreasing the physical work required for each test session. This would likely lead to improved patient compliance within each test session, decreased side effects, and, ultimately, increased participation in surveillance programs. An early warning signal based on EV/FEV₃ could be incorporated into spirometry software to alert the operator to a possible hesitating start. This could be very beneficial for testing technicians who suspect a hesitating start but desire additional information.

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Dr McKay: contributed to concept development; performance of spirometry interpretations; quality control for all testing conducted at the FWMMP; training of testing technicians who administered tests; writing and/or revision of the manuscript; and provision of technical assistance with data collection, clean-up, and analysis.

Dr Freeman: contributed to critical revision of the manuscript.

Dr Levin: contributed to statistical methods and analysis and writing and revision of the manuscript.

Dr Pinney: contributed to data acquisition (including recruitment of subjects); the IRB protocol; obtaining of consents; input into the quality assurance program at the FWMMP; the yearly exam protocols, including the selection of tests to be performed for the FWMMP; and critical revision of the manuscript.

Ms Alshaikh: contributed to data management, statistical support, and review of the manuscript.

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