Bronchodilator Response in Patients With Normal Baseline Spirometry

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BACKGROUND: Spirometry before and after bronchodilator is performed to assess air flow-limitation reversibility. In patients with normal baseline spirometry the frequency of a positive bronchodilator response, as defined by American Thoracic Society/European Respiratory Society criteria, has not been described. METHODS: We retrospectively analyzed adult patients tested in 2 academic pulmonary function testing laboratories over a 7-year period, with specific attention to patients who underwent bronchodilator testing after a normal baseline spirometry (FEV_1, FVC, and FEV_1/FVC within normal limits). The frequency of a positive response to bronchodilator, defined as a 12% and 200 mL increase in either FEV_1 or FVC, was calculated and associated with demographic factors. RESULTS: Of the 1,394 patients with normal spirometry who were administered bronchodilator, 43 (3.1%) had a positive response. The percent of patients responding to bronchodilator were grouped according to pre-bronchodilator FEV_1: > lower limit of normal to 90% of predicted = 6.9%, 90–100% of predicted = 1.9%, and > 100% of predicted = 0%. An FEV_1/FVC in the lowest 2 quartiles was associated with a higher frequency of bronchodilator response. Older patients were more likely to respond to bronchodilator, but no other demographic factors were associated with a positive bronchodilator response. CONCLUSIONS: In our study population the frequency of a positive bronchodilator response in patients with normal baseline spirometry is 3.1%. None of the patients with a pre-bronchodilator FEV_1 > 100% of predicted and only 1.9% of patients with an FEV_1 between 90% and 100% of predicted responded. Bronchodilator testing can be omitted in patients with normal spirometry and an FEV_1 above 90% of predicted, as they have a low probability of a positive response. *Key words: spirometry; lung function testing; bronchodilation; FEV_1.* [Respir Care 2012;57(10):1564–1570. © 2012 Daedalus Enterprises]

Introduction

Pulmonary function laboratories commonly administer an inhaled bronchodilator to determine if reversible airflow limitation is present. Spirometry measurements before and after short-acting bronchodilator administration are recommended in the diagnosis of asthma[1] and COPD.[2] Many clinicians routinely order pre- and post-bronchodilator testing, regardless of pre-bronchodilator results, though adding the bronchodilator substantially increases time and expense. Prior studies have analyzed the response to bronchodilator in subjects with normal lung function.[3–7] However, we know of no other studies that have described the frequency of a positive bronchodilator response in a large group of patients with normal baseline spirometry, using the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on the Standardiza-

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tion of Lung Function Testing definition of a "significant" bronchodilator response (ie, an increase of at least 12% and 200 mL in FVC or FEV_1, compared with baseline values).[8]

The primary aim of this study was to determine if bronchodilator administration can be omitted in patients with normal baseline spirometry who have a low probability of responding to bronchodilator. We address this question by quantifying the frequency of a positive bronchodilator response in patients with normal baseline spirometry and then examining demographic factors to see which, if any, are associated with a positive change in spirometry after bronchodilator. Some results have previously been reported in abstract form.[9]

QUICK LOOK

Current knowledge

Spirometry before and after bronchodilator is performed to assess the reversibility of air-flow limitation in patients with reactive airway disease. In patients with normal baseline spirometry, the frequency of a positive bronchodilator response, as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria, has not been described.

What this paper contributes to our knowledge

Patients with baseline spirometry within normal limits and an $FEV_1 > 90\%$ of predicted rarely respond to bronchodilators. Omitting routine bronchodilator testing in these patients can improve pulmonary laboratory efficiency and decrease costs.

Methods

Test Performance

All tests were performed at the pulmonary function laboratories at LDS Hospital and Intermountain Medical Center, from 2002 through 2008, using one of 4 Sensormedics/Viasys instruments (Yorba Linda, California). Instruments were maintained according to the manufacturer's recommendations, including daily calibration with a 3-L syringe. The instruments were also periodically tested with a waveform generator (PWG, MH Custom Designs, Salt Lake City, Utah) for accuracy and precision, as part of an ongoing quality control program.

All tests were conducted by one of 5 certified pulmonary function technicians. Subjects were tested in a sitting position, using nose clips. Post-bronchodilator spirometry was performed if requested by the ordering physician. For testing bronchodilator response, 400 μg of albuterol was given in 4 separate 100 μg doses with a metered-dose inhaler and a spacer device for all tests done after 2005. Before and including 2005, 300 μg of albuterol was used. Doses were given at 30 second intervals. Post-bronchodilator spirometry was performed 15 min after the albuterol was administered. The largest FVC and FEV_1 from both the pre- and post-bronchodilator trials were recorded. All tests were examined for ATS/ERS acceptability and repeatability criteria in use at the time.[10,11] Specifically, test criteria included a satisfactory start of test, with a back extrapolated volume < 0.150 L or 5% of FVC, forced exhalation time ≥ 6 seconds, and adequate repeatability, with the highest and next highest FVC and FEV_1 within 200 mL (studies obtained between 2002 and 2005) and 150 mL (studies obtained between 2006 and 2008) of each other. Tests that did not meet acceptability and repeatability criteria were excluded.

Subject Selection

We retrospectively analyzed all spirometry data from patients referred to the pulmonary function laboratories at LDS Hospital and Intermountain Medical Center from 2002 through 2008. Data from patients age 18 years or older with acceptable and repeatable test results were included. From this database, the following subsets were determined: patients who received bronchodilator; patients with a positive response to bronchodilator, as defined by the ATS/ERS Task Force criteria (a 12% and 200 mL improvement in either FEV_1 or FVC); patients with a pre-bronchodilator FEV_1, FVC, and FEV_1/FVC that were within predicted limits, defined as being greater than the lower limit of normal, using the National Health and Nutrition Examination Survey (NHANES III) reference values,[10] and a positive response to bronchodilator. For patients who had multiple studies in the laboratory, only the first test was used for analysis. The study was approved by the institutional review board (Intermountain Healthcare Office of Research, IRB 1010237); patient consent was waived for this retrospective study. No personal identifying data were collected for this analysis.

Statistical Analysis

Pre- and post-bronchodilator spirometry results were analyzed by calculating the mean volume change, percentage change, and a 95% CI for FEV_1 and FVC for the entire cohort and for subsets including sex, age by quartile, body mass index by quartile, pre-bronchodilator FEV_1/FVC percent of predicted by quartile, and pre-bronchodilator FEV_1 divided into 3 groups: $>$ lower limit of normal to 90% of

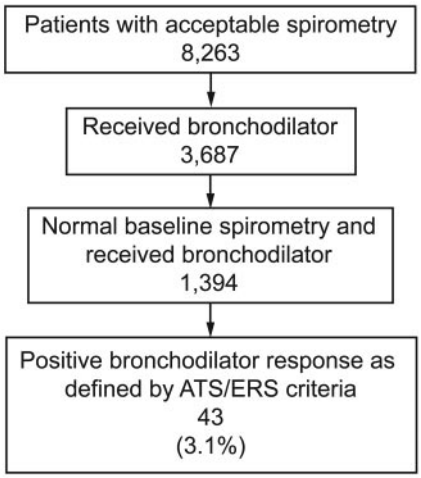

Fig. 1. Patient flow through study is illustrated. ATS/ERS = American Thoracic Society/European Respiratory Society.

predicted, > 90% of predicted to 100% of predicted, and > 100% of predicted. The tests were also analyzed by testing date, comparing those obtained through 2005 versus those obtained after 2005, when the laboratory procedure changed from administering 300 μg to 400 μg of albuterol. A histogram was created for the percent change in FEV_1 and FVC for the entire cohort. The number of patients with a positive bronchodilator response based on improvement in FEV_1 or FVC was determined. The number of patients with a pre-bronchodilator FEV_1/FVC within predicted limits and a post-bronchodilator ratio less than the lower limit of normal was determined.

The Shapiro-Francia W test was used to determine that the change in FEV_1 and FVC with bronchodilator was not normally distributed. The Kruskel-Wallis test was used to determine if the change in FEV_1 and FVC following bronchodilator administration was significant among subgroups. The Fisher exact test was used to determine if the number of patients responding to bronchodilator among subgroups was significant.

Results

Subject selection and flow are listed in Figure 1. After excluding 2% of patients who did not meet ATS/ERS acceptability and repeatability criteria in use at the time of testing, there were 8,263 patients who underwent spirometry at LDS Hospital and Intermountain Medical Center between 2002 and 2008. Of these, 3,687 (45%) received bronchodilator, as requested by the ordering clinician. Of the patients who received bronchodilator, 1,394 (38% of patients receiving bronchodilator) had normal baseline spirometry, and 43 out of 1,394 (3.1% of patients with normal spirometry administered bronchodilator) had a "significant" response to bronchodilator, using ATS/ERS criteria.[8] Demographic and pre-bronchodilator spirometry results for responders and non-responders are detailed in Table 1. Of the 43 patients with a positive response to bronchodilator, 32 patients responded based on FEV_1 criteria, 6 patients responded based on FVC criteria, and 5 patients met both response criteria. The patients who responded to bronchodilator based on FVC criteria did not have an appreciably longer forced exhalation time (9.1 s pre-bronchodilator vs 10.0 s post-bronchodilator).

Table 1. Demographic and Pre-bronchodilator Spirometry Results

Subject Demographics	Positive	Negative
Age, y	63.2 ± 15.9	53.3 ± 16.2
Male/female	22/21	638/713
Race, no. (%)		
White	40 (93.0)	1,256 (93.0)
African American	1 (2.3)	11 (0.8)
Hispanic	1 (2.3)	50 (3.7)
Asian	0	15 (1.1)
Other*	1 (2.3)	19 (1.4)
Body mass index, kg/m^2	30.88 ± 7.23	29.22 ± 6.52
FEV_1, L	2.42 ± 0.82	3.05 ± 0.85
FEV_1, % predicted	84.87 ± 6.08	96.25 ± 13.11
FVC, L	3.43 ± 1.11	4.02 ± 1.07
FVC, % predicted	91.60 ± 7.08	99.36 ± 12.60
FEV_1/FVC	0.704 ± 0.042	0.758 ± 0.056
FEV, FVC, % predicted	92.50 ± 3.61	96.83 ± 6.00

± Values are mean ± SD.
* Includes Middle Eastern, Tongan, Pacific Islander, Polynesian, Native American, and not specified.

The responses to bronchodilator for the patients grouped according to pre-bronchodilator FEV_1 percent of predicted (> lower limit of normal to 90% of predicted, > 90% of predicted to 100% of predicted, and > 100% of predicted) are listed in Table 2. Patients with the lowest pre-bronchodilator FEV_1 percent of predicted had larger volume and percent increases in FEV_1 and FVC with bronchodilator administration ($P < .05$). No one with a pre-bronchodilator FEV_1 > 100% of predicted responded to bronchodilator; 6.9% of the patients with a pre-bronchodilator FEV_1 > lower limit of normal to 90% of predicted responded to bronchodilator; and 1.9% of patients with a pre-bronchodilator FEV_1 > 90% to 100% of predicted responded to bronchodilator.

The responses to bronchodilator based on FEV_1/FVC percent of predicted are listed in Table 3. There were significant differences among the quartiles in the change in FEV_1 following bronchodilator administration ($P < .01$). The change in FVC with bronchodilator was of borderline significance ($P = .056$). Patients with lower FEV_1/FVC percent of predicted had larger increases in FEV_1 and FVC. Also, patients with lower FEV_1/FVC were more likely to meet criteria for bronchodilator response, com-

Table 2. Bronchodilator Responses for Subjects With Pre-bronchodilator Spirometry Within Normal Limits

Pre-bronchodilator FEV_1 (% predicted)	With Response to Bronchodilator no. (%)	Change in FEV_1 mean (95% CI), mL	Change in FEV_1 mean (95% CI), %	Change in FVC mean (95% CI), mL	Change in FVC mean (95% CI), %
> 100 (n = 429)	0	61.1 (48.2–74.0)	1.84 (1.48–2.20)	−35.4 (−47.0 to −23.8)	−0.79 (−1.05 to −0.53)
90–100 (n = 472)	9 (1.9)	85.6 (73.5–97.7)	2.79 (2.41–3.17)	−4.7 (−17.0 to 7.6)	−0.11 (−0.41 to 0.19)
> lower limit of normal to 90 (n = 493)	34 (6.9)	97.4 (86.0–108.8)	3.81 (3.37–4.25)	27.5 (14.2–40.8)	0.84 (0.45–1.23)

Table 3. Change in FEV_1 and FVC After Administration of Bronchodilator by Quartile of Percent Predicted FEV_1/FVC

Quartile	Pre-bronchodilator FEV_1/FVC (% predicted)	Meeting Bronchodilator Response Criteria* no. (%)	Change in FEV_1 mean ± SD mL	Change in FEV_1 mean ± SD %	Change in FVC mean ± SD mL	Change in FVC mean ± SD %
1 (n = 348)	87–91	25 (7.2)	122.0 ± 14.6	4.3 ± 0.5	5.5 ± 15.7	0.2 ± 0.4
2 (n = 349)	92–95	13 (3.7)	96.4 ± 13.7	3.3 ± 0.5	11.7 ± 13.2	0.3 ± 0.4
3 (n = 349)	96–101	5 (1.4)	72.2 ± 12.2	2.5 ± 0.4	−10.7 ± 16.4	−0.2 ± 0.4
4 (n = 348)	102–129	0	38.4 ± 13.2	1.4 ± 0.4	−17.5 ± 12.9	−0.3 ± 0.3
Total	(n = 1,394)	43 (3.1)	82.3 ± 7.0	2.9 ± 0.2	−2.7 ± 7.3	0.0 ± 0.2

* 12% and 200 mL increase in FEV_1 or FVC.

pared with those with a higher FEV_1/FVC ($P < .01$). Combining the 2 lowest quartiles of FEV_1/FVC percent of predicted (87–95%), 5.5% of patients responded to bronchodilator, versus 0.7% for patients with an FEV_1/FVC percent of predicted in quartiles 3 and 4 (96–129%).

For the entire cohort, the mean change in FEV_1 was 82.3 mL (95% CI 75.2–89.3 mL) or 2.9% (95% CI 2.6–3.1%). The mean change in FVC was −2.7 mL (95% CI −10.1 to 4.7 mL) or 0% (95% CI −0.2 to 0.2%). The percent change in FEV_1 and FVC for all patients with normal pre-bronchodilator spirometry are shown as a histogram (Figs. 2 and 3) and graphically (Figs. 4 and 5).

There was no significant difference in the mean change in FEV_1 and FVC or in the percentage of patients responding to bronchodilator between 2002 and 2005 and 2006 and 2008 when the laboratory procedure changed from administering 300 μg to 400 μg of albuterol to test for bronchodilator response. We found no significant difference in bronchodilator response based on body mass index. There was a significant difference in number of patients responding to bronchodilator based on quartile of age ($P < .01$), with patients in the oldest quartile (age 65–95 years) more likely to respond to bronchodilator. Table 4 provides the number of patients in 10 year increments of age and the percent meeting bronchodilator response criteria. Men had a significantly larger absolute increase in FEV_1 with administration of bronchodilator than women (109 mL [95% CI 97–120 mL], compared to 58 mL [95% CI 50–67 mL]) ($P < .01$). However, the percentage increase in FEV_1 was not significantly different for men and women (3.2% [95% CI 2.9–3.6%] and 2.5% [95% CI 2.2–2.8%]), respectively ($P = .34$). There was no significant difference between men and women in change in FVC with administration of bronchodilator ($P = .12$). There was also no significant difference in the percent of men (3.3%), compared with women (2.9%), who met the criteria for bronchodilator responsiveness ($P = .61$).

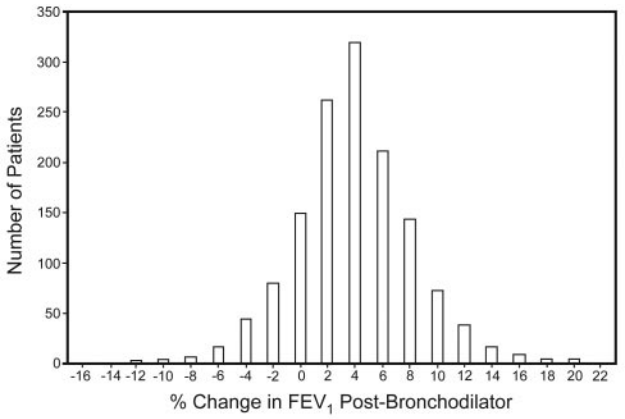

Fig. 2. Histogram with percent change in FEV_1 post-bronchodilator for patients with normal pre-bronchodilator spirometry.

Of the 1,373 patients with a normal FEV_1, FVC, and FEV_1/FVC who received bronchodilator, 21 (1.5%) had a post-bronchodilator FEV_1/FVC below the lower limit of normal. These patients had a mean reduction in FEV_1 of 111 mL and a mean increase in FVC of 46 mL. For patients with normal spirometry who received a broncho-

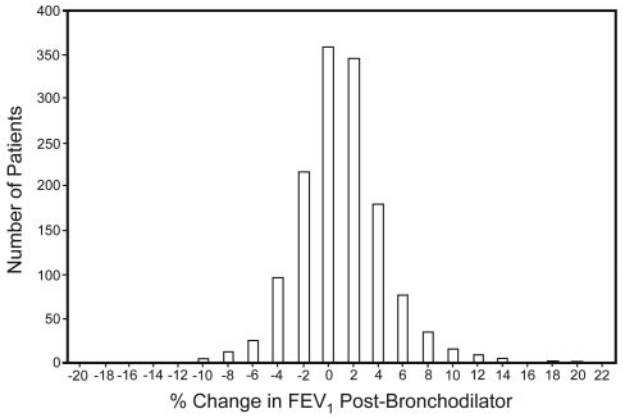

Fig. 3. Histogram with percent change in FVC post-bronchodilator for patients with normal pre-bronchodilator spirometry.

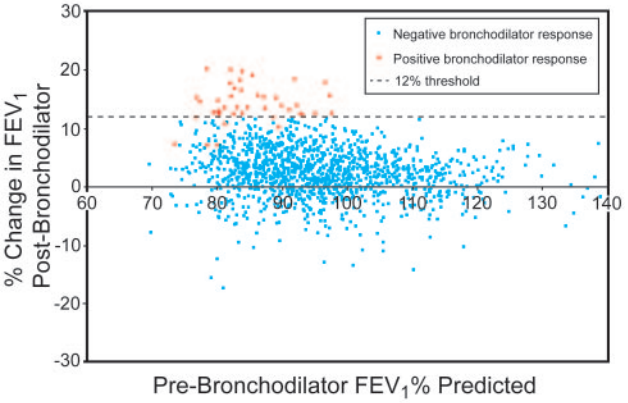

Fig. 4. Figure demonstrating percent change in FEV_1 post-bronchodilator in relation to pre-bronchodilator FEV_1 percent of predicted in patients with normal baseline spirometry.

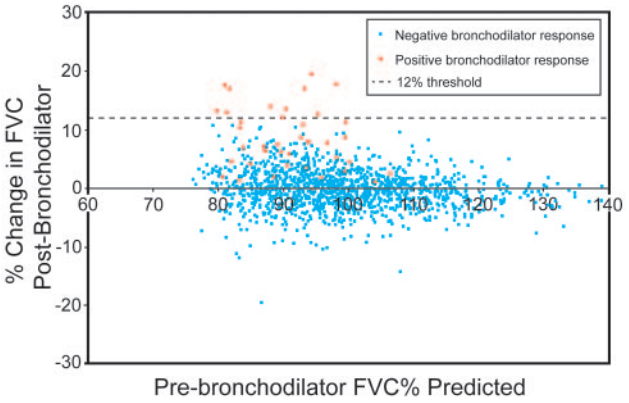

Fig. 5. Figure demonstrating percent change in FVC post-bronchodilator in relation to pre-bronchodilator FVC percent of predicted in patients with normal baseline spirometry.

Table 4. Bronchodilator Response Based on Age

Subject Age Range, y	Subjects, no. (%)	% Meeting Bronchodilator Response Criteria*
18–25	63 (4.5)	1.6
26–35	131 (9.4)	0.8
36–45	200 (14.3)	1.0
46–55	315 (22.6)	2.5
56–65	321 (23.0)	2.8
66–75	208 (14.9)	5.3
76–85	134 (9.6)	7.5
86+	22 (1.6)	4.5

* 12% and 200 mL increase in FEV_1 or FVC.

dilator, 11 (0.8%) had a reduction in $FEV_1 > 10\%$, and 8 patients (0.6%) had a decrease in FVC $> 10\%$.

Discussion

Many clinicians routinely order pre- and post-bronchodilator testing without regard to pre-bronchodilator results. In our hospital based pulmonary function testing labs, bronchodilator testing was requested in 45% of patients. It is likely that a higher percentage of patients undergo bronchodilator testing in hospital based labs, compared with clinic labs, due to time constraints in clinic based pulmonary labs. The frequency of a positive response to bronchodilator, as defined by the ATS/ERS Task Force criteria[8] (increases of $> 12\%$ and 200 mL in either FEV_1 or FVC), in patients with normal pre-bronchodilator spirometry has not been previously described. We found that 3.1% of patients with normal baseline spirometry responded to bronchodilator, based on ATS/ERS Task Force criteria.[8] The pre-bronchodilator percent of predicted FEV_1 and percent of predicted FEV_1/FVC both predicted bronchodilator responsiveness.

In our study, no patient with a pre-bronchodilator $FEV_1 > 100\%$ of predicted, and only 1.9% of patients with a pre-bronchodilator FEV_1 between 90–100% of predicted met bronchodilator response criteria. Less than 1% of patients with an FEV_1/FVC percent of predicted in the 3rd and 4th quartile, corresponding to an FEV_1/FVC percent of predicted $> 95\%$, responded to bronchodilator. Older patients were also more likely to respond to bronchodilator, but none of the other demographic factors collected for spirometry (height, weight, sex) reliably predicted a response to bronchodilator.

We propose that standard pulmonary function laboratory practice should be to forgo bronchodilator testing in patients when FEV_1, FVC, and FEV_1/FVC are all within normal limits and the baseline FEV_1 is $> 100\%$ of predicted. A positive response is also unlikely when the FEV_1 is between 90 and 100% of predicted. We have concen-

trated on the FEV_1 because it is a more practical measure for routine clinical use. FEV_1 is highly repeatable[11] and, unlike FEV_1/FVC, is not dependent on exhalation time.

Omitting bronchodilator testing in patients with a low probability of responding would decrease healthcare costs and improve pulmonary laboratory efficiency. Spirometry performed before and after inhaled bronchodilator testing, Current Procedural Terminology (CPT) code 94060, is assigned a relative value unit (RVU) 1.88 times that of spirometry without bronchodilator responsiveness testing, CPT code 94010.[12] Using a pre-bronchodilator FEV_1 threshold of 90% of predicted in our laboratories would have resulted in 901 patients (24% of all patients who received bronchodilator) not receiving bronchodilator and would have missed only 9 patients with positive responses (0.6% of all patients with normal spirometry receiving bronchodilator).

Bronchodilator responsiveness has been studied in the general population.[3–7] In a population study performed on generally healthy subjects, Dales et al found the upper 95th percentile for bronchodilator response for FEV_1 and FVC to be approximately 9%.[4] Kainu et al evaluated the FEV_1 response to bronchodilation in an urban population sample, using the same dose and delivery method of albuterol (400 μg) as was used after 2005 in our laboratories.[7] They found a mean FEV_1 change (77 mL vs 82 mL) and percent change (2.5% vs 2.9%) comparable to our patients, and, also similar to our results, that the baseline FEV_1/FVC had a strong influence on the change of FEV_1 after bronchodilator. We found a negative relationship between baseline FEV_1 and bronchodilator response, as have several other investigators.[3–5,7] The magnitude and consistency of the negative relationship between pre-bronchodilator FEV_1 and bronchodilator response suggest that this finding is not primarily due to regression to the mean.

Prior studies have produced inconsistent results regarding demographic factors and bronchodilator response. We did not find a consistent relationship between sex or body mass index in the percent increase in FEV_1 or FVC. In our cohort, older patients were more likely to respond to bronchodilator. Age has been found to have a negative correlation,[7] positive correlation,[5] or no correlation[13] with FEV_1 response to bronchodilator. Similar to our findings, other studies have noted a larger absolute increase in FEV_1 with males, compared with females, but no change in the percent increase.[5,7] None of the prior studies specifically addressed the frequency of bronchodilator response or the factors associated with bronchodilator responsiveness using ATS/ERS Task Force criteria.

We found that 1.5% of the patients tested converted from having a normal FEV_1/FVC pre-bronchodilator to a ratio less than the lower limit of normal post-bronchodilator, meeting the spirometric criteria for obstruction.[8] This "negative bronchodilator response" was noted in 0.5% of subjects in a population sample, using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for obstruction (FEV_1/FVC < 0.70).[6] In addition, 0.8% of our patients had a reduction of $> 10\%$ in FEV_1. A significant reduction in lung function after administration of bronchodilator, termed paradoxical bronchoconstriction, has been previously reported.[14–16]

We do not suggest that all patients with normal baseline spirometry forgo bronchodilator testing. In our study, the group of patients whose FEV_1 was above the lower limit of normal but $< 90\%$ of predicted had a bronchodilator response rate of 6.9%. A positive response to bronchodilator indicates the presence of reversible air-flow limitation and may have important diagnostic and treatment implications. However, the clinical utility of a bronchodilator response in distinguishing asthma from other diseases, such as COPD, bronchiectasis, cystic fibrosis, or bronchiolitis, is not clear.[17–19] It is also important to recognize that the ATS/ERS Task Force criteria for bronchodilator responsiveness are much debated and the current standard for defining a positive response is somewhat arbitrary, based on available evidence.[3–7] The current ATS/ERS Task Force criteria for bronchodilator response are based more on expert opinion than scientific evidence.

Limitations

Our study does not include clinical information such as smoking status. The study was obtained in a state with a low smoking prevalence (Utah). This limits our ability to comment on which clinical characteristics may help predict bronchodilator responsiveness. Our laboratory protocol changed from administering 300 μg to 400 μg of inhaled albuterol to test for bronchodilator responsiveness in 2006, in response to the recommendations of the ATS/ERS Task Force.[20] We found no difference in the percentage of patients responding to bronchodilator or in changes in FEV_1 or FVC after the change in dose. Many pulmonary function laboratories use different doses, delivery methods, and bronchodilator agents to test for bronchodilator responsiveness, and our results may not apply to these labs. Our study may also have a referral bias. Bronchodilator testing was performed only if requested by the referring clinician. While some clinicians request bronchodilator testing for all patients, others may be more selective and order bronchodilator testing only for the patients they suspect of having a higher probability of reversible air-flow limitation. Finally, the study population was primarily white (93%). It is not clear if these results are applicable to other ethnic groups.

Conclusions

Our results indicate that patients with baseline spirometry within normal limits and an $FEV_1 > 100\%$ of pre-

dicted do not respond to bronchodilator, and those with an $FEV_1 > 90\%$ of predicted are unlikely to respond to bronchodilator. Omitting routine bronchodilator testing in these patients will improve pulmonary laboratory efficiency and decrease the cost to patients. Our lab policy is to no longer perform bronchodilator testing on patients with a pre-bronchodilator FEV_1/FVC that is within predicted limits and an FEV_1 that is $> 100\%$ of predicted.

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