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ORIGINAL ARTICLE

# Forced Expiratory Time and Bronchial Hyperresponsiveness to Methacholine

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## ABSTRACT

*Pulmonary function tests (PFTs) are normally performed prior to methacholine inhalation challenges (MICs). In contrast to normal baseline spirometry ($FEV_1$, $FEF_{25\%–27\%}$, FVC), we have observed patients with positive MICs having shortened forced expiratory times ($FET_{100\%}$) in the baseline pre-MIC PFT. We prospectively evaluated the correlation of abnormalities in baseline pre-MIC $FET_{100\%}$ in patients who have positive vs. negative MICs. Prospective analysis of baseline pre-MIC $FET_{100\%}$ and MIC results in suspected asthmatics with normal lung exams, spirometry and chest x-rays. Using a $PC_{20}$ $FEV_1$ of $\leq 8$ mg/ml methacholine, there were 115 positive and 69 negative MICs. The mean ($\pm 1$ SD) $FET_{100\%}$ in the positive MIC group was $3.57 \pm 1.68$ sec vs. $4.73 \pm 1.60$ sec in the negative group. The difference in these means was statistically significant ($p < 0.0001$). There was a statistically significant difference in the incidence of $FET_{100\%} < 4$ sec in the positive (55.65%) vs. the negative (30.43%) MIC group, $p < 0.001$. There was also a statistically*

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*significant difference in the incidence of positive MIC in $FET_{100\%} < 4$ sec (75.29%) vs. $FET_{100\%} \geq 4$ sec (51.52%), $p < 0.001$. Our results suggest that in our highly selected, well-characterized population, $FET_{100\%} < 6$ sec is common and $FET_{100\%} < 4$ sec correlates with an increased likelihood of having a positive MIC.*

***Key Words:*** *Forced expiratory time ($FET_{100\%}$); Methacholine inhalation challenge (MIC); Pulmonary function test (PFT)*



## INTRODUCTION

Bronchoprovocation challenges with methacholine have become important techniques for evaluating patients with asthma-like symptoms and normal spirometry. The benchmark for measuring responses during methacholine inhalation challenge (MIC) has been the $FEV_1$, although previous work done has documented enhanced sensitivity using a cluster of pulmonary function test (PFT) parameters including $FEV_1$, FVC, $FEF_{25\%-75\%}$, specific airways conductance (sGaw), and thoracic gas volume (TGV) (1,2). Although counterintuitive, we have previously observed that in a large number of complete PFTs done prior to MICs, many patients with positive MICs had a shortened forced expiratory time ($FET_{100\%}$) (3). We hypothesize that a shortened baseline pre-MIC $FET_{100\%}$ (< 4 sec) may significantly correlate with a positive MIC in this patient population. The purpose, therefore, of this study is to prospectively analyze whether in a well-characterized group of individuals, baseline pre-MIC $FET_{100\%} < 4$ sec correlates with methacholine reactivity. If this holds true, then $FET_{100\%} < 4$ sec in a select group of individuals with lower respiratory symptoms may help identify individuals who are likely to have methacholine-sensitive airways.

## METHODS AND MATERIALS

### Subjects

A prospective analysis of MIC results from our pulmonary function laboratory was performed from January 1998 to March 2000. Patients coming in for MIC had asthma-like symptoms of recurrent or persistent nonproductive cough, dyspnea and/or chest tightness. Patients had a baseline $FEV_1$% predicted value ≥80%, $FEV_1$/FVC ratio ≥80%, $FEF_{25\%-75\%}$ predicted value ≥80%, and FVC% predicted value ≥80%. Those PFTs that did not satisfy American Thoracic Society (ATS) criteria for acceptability and reproducibility (except in regard to a forced expiratory maneuver of at least 6 sec) were excluded from this study (1). There were 62 male and 122 nonpregnant female patients aged 5–80 years (22 patients <12 years, 17 patients ≥12 and <18 years, 145 patients ≥18 years) with a mean age of 35 years. Symptoms were present for at least three months prior to MIC. No patients were identified in this study at the time of testing with a diagnosis of anemia, polycythemia, congestive heart failure, emphysema, chronic bronchitis, cystic fibrosis, sarcoidosis or bronchiectasis, or other primary lung diagnoses, with the exception of possible asthma. All patients had normal chest physical examinations and chest radiographs. Each patient was evaluated clinically following MIC over a period of 4–12 months to determine his or her subsequent clinical evolution of symptoms. The history, physical examinations, and follow-up were performed by three of the investigators (M.G., D.D., E.D.).

### Pulmonary Function Test

Complete PFTs for all subjects were performed by the same technician certified in pulmonary function testing by the National Board for Respiratory Care and supervised by one of the authors (M.F.G.). A Sensormedics 2200/6200 system spirometer and variable pressure constant volume body plethysmography (Sensormedics; Yorba Linda, CA) was used. The spirometer was calibrated daily with a 3 L syringe. Volume–time curves, flow–volume curves, expiratory flow rates, and forced expiratory time ($FET_{100\%}$) were generated through standard techniques using a computer-assisted spirometer with the patient in a sitting position. Forced expiratory maneuvers were performed in triplicate

and the best efforts were analyzed. Patients were instructed and vigorously coached to deeply inspire followed by a hard, fast, and prolonged forced expiration for at least 6 sec or until expiration ceased. The PFT data were expressed in both absolute terms and as a percentage of predicted normal values. All lung volumes and flow rates were reported BTPS. Acceptable peak flow was $\geq$80% of predicted and the two best $FEV_1$ were within 15% of each other. All patients had normal spirometric measurements defined by $FEV_1 \geq 80\%$ of predicted normal values, $FEV_1/FVC$ ratio $\geq$80%, $FEF_{25\%-75\%} \geq 80\%$ of predicted normal values, and $FVC \geq 80\%$ of predicted normal values.

### Methacholine Inhalation Challenge

Those patients who were smokers avoided smoking for at least 12 hr prior to MIC. Patients did not have symptomatic respiratory infection within six weeks of the MIC. Aeroallergen exposure was not controlled except in obvious cases of animal sensitivity. No study patient received recent influenza or rubella immunizations. Medication that could interfere with MIC test results was discontinued prior to MICs as follows: theophyllines and antihistamines were withheld for at least 48 hr; $beta_2$ agonists, cromolyn, nedocromil and leukotriene modifiers were withheld for at least 12 hr. Inhaled corticosteroids were withheld for four weeks prior to the study. No patients were on oral steroids at the time of the MIC. Patients were not taking erythromycin, beta-blockers, or ACE inhibitors at the time of the challenge. Exercise and excessive exposure to cold air were avoided for at least 2 hr before the MIC. Ingestion of coffee, cola, or chocolate drinks was avoided for at least 6 hr prior to testing.

The protocol for MIC closely followed recommendations made by the Canadian Thoracic Society (4) and as previously reported by us (2). As a control, 3 mL of normal saline solution was initially inhaled by tidal volume breathing for 2 min. The saline control was followed by increasing concentrations of methacholine solutions at 5 min intervals beginning with 0.03 mg/mL followed by concentrations of 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, and 25.0 mg/mL. Three milliliters of each concentration were administered and inhaled by the participant for 2 min. A Sensormedics system (Yorba Linda, CA) 2200 spirometer and 6200 system variable pressure constant volume body plethysmograph was used. Changes in $FEV_1$, $FEF_{25\%-75\%}$, and FVC were recorded 30 sec and 90 sec after each inhalation dose. The maneuver with the highest $FEV_1$ was recorded. The MIC continued until the $FEV_1$ fell to 20% or more below saline baseline control or the highest concentration of methacholine had been reached. Nebulized bronchodilator was given at the completion of the test if the challenge was positive or if the patient became significantly symptomatic. The same technician performed the MIC for all the participants. A positive response was defined as 20% or greater fall in $FEV_1$ at $\leq$8 mg/mL of methacholine. The 8 mg/mL cutoff was chosen based on earlier observations (2,5,6).

Study patients completing an MIC were followed and treated for at least four months. A physician-based diagnosis of asthma was made or ruled out based on the diagnostic testing and response to medical therapy. Informed consent was obtained from all participants. Participants were offered no honorarium.

### Statistical Analyses

All statistical analyses were performed with the JMP, IN statistical package (SAS Institute Inc., Cary, North Carolina). Descriptive statistics were used to define group mean, standard deviation, and range of pre-MIC $FET_{100\%}$ in patients with positive vs. negative MICs. A two-sample *t*-test was applied to see if there was a significant difference in mean pre-MIC $FET_{100\%}$ responses between MIC positive patients and MIC negative patients. A contingency table ($2 \times 2$) was constructed for MIC results and the baseline pre-MIC $FET_{100\%}$ results. The incidence rate of $FET_{100\%} < 4$ sec in patients with positive vs. negative MICs was calculated, as was the incidence rate of positive MIC in patients with $FET_{100\%} <$ 4 sec vs. $FET_{100\%} \geq 4$ sec. The rates were then statistically compared by the inference for sample proportion technique to see if there were significant differences in these incidences. A chi-square test was carried out to evaluate whether there was a significant association between the baseline pre-MIC $FET_{100\%}$ and the occurrence of a positive or negative MIC.

## RESULTS

One hundred and eighty-four complete baseline PFTs and MICs were performed in a population

of patients with symptoms suggestive of asthma. The baseline pre-MIC studies were completed without adverse event. Although most patients presented with symptoms of cough, coughing did not significantly interfere with the performance of the tests in almost all cases. A stuttering pattern of the expiratory phase of the flow–volume loop, consistent with coughing, was not seen in any of the baseline pre-MIC tests used for this study. In addition, forced expiratory maneuvers were not abbreviated in the baseline pre-MIC tests due to unsatisfactory start of expiration, second inspiration, Valsalva maneuver, leak, or an obstructive mouthpiece (i.e., tongue or dentures in front of mouthpiece); if so, the test was noted by the technician and deleted from this analysis. Technical performance of the baseline tests were adequate and consistent with ATS criteria as noted by technician comments, with the exception that a forced expiration of less than 6 second due to breath cessation was accepted (1). There were no statistically significant differences in $FEV_1$, $FEV_1/FVC$ ratio, $FEF_{25\%–75\%}$, and FVC in subjects with positive vs. negative MIC. (Data not shown but available through e-mail correspondence.) There were no severe immediate or delayed reactions during or after MICs. Results were analyzed and patients were divided into two groups: positive or negative MIC responses. Sixty-nine of this very selective patient population had negative MICs defined by the absence of a 20% threshold decrease in $FEV_1$ by the $\leq 8$ mg/mL cutoff dose. One hundred and fifteen patients had positive MICs defined by a 20% decrease in $FEV_1$ at a methacholine dose of $\leq 8$ mg/mL.

A $2 \times 2$ contingency table of MIC results and $FET_{100\%}$ values is shown in Table 1. Aggregate data including group mean, standard deviation, and range for pre-MIC $FET_{100\%}$ in patients with positive and negative MICs are shown in Table 2. Although the raw data were not normally distributed, the sample size was large enough to compare the two sample means using a two-sample *t*-test. The results of a two-sample *t*-test comparing the mean pre-MIC $FET_{100\%}$ in positive ($3.57 \pm 1.68$ sec) vs. negative ($4.73 \pm 1.60$ sec) MIC groups showed a statistically significant difference, $p < 0.0001$ (Table 2 and Fig. 1).

***Table 1***

*Contingency Table*

| | $FET_{100\%}$ $<4$ sec | $FET_{100\%}$ $\geq 4$ sec | Totals |
|---|---|---|---|
| Positive MIC | 64 | 51 | 115 |
| Negative MIC | 21 | 48 | 69 |
| Totals | 85 | 99 | 184 |

The incidence of a baseline pre-MIC $FET_{100\%} < 4$ sec was significantly higher in the positive (55.65%) vs. negative (30.43%) MIC subject group by the inference for sample proportion technique, $p < 0.001$ (Table 2). The incidence of a baseline pre-MIC $FET_{100\%} \geq 4$ sec was significantly higher in the negative (69.57%) vs. positive (44.35%) MIC group by the inference for sample proportion technique, $p < 0.001$ (Table 2). In addition, the incidence of a positive MIC was significantly higher in patients with $FET_{100\%} < 4$ sec (75.29%) vs. $FET_{100\%} \geq 4$ sec (51.52%), $p < 0.001$. The incidence of a negative MIC was significantly higher in patients with $FET_{100\%} \geq 4$ sec (48.48%) vs. $FET_{100\%} < 4$ sec (25.61%), $p < 0.001$. A chi-square test evaluating the significance of an association between the baseline pre-MIC $FET_{100\%}$ and the occurrence of a positive MIC revealed that an $FET_{100\%} < 4$ sec was significantly associated with positive MICs ($p < 0.009$).

## DISCUSSION

Methacholine inhalation challenge has been established as a sensitive and specific test of airways hyperreactivity in asthmatic patients (2,7). The value of an MIC, in part can also be related to its ability to objectively define the presence of airways hyperreactivity for which therapeutic intervention can then be instituted. Few researchers have reported the association of baseline nonspirometric pre-MIC PFT parameters and methacholine sensitivity (8–12).

In our sample of a well-characterized, selected patient population with normal baseline values of $FEV_1$, $FEF_{25\%–75\%}$, and FVC, there was variability and overlap in $FET_{100\%}$ measurements in the positive vs. negative MIC groups. Despite this, we were able to identify several statistically significant associations between the baseline pre-MIC $FET_{100\%}$ and MIC responses. The incidence of $FET_{100\%} < 4$ sec in the baseline pre-MIC PFT was significantly more common in positive (55.65%) vs. negative (30.43%) MICs ($p < 0.001$) (Table 2). An $FET_{100\%} < 4$ sec was significantly associated with a positive MIC

***Table 2***

*Range, Mean, Incidence, and Statistical Significance of Difference Between Positive Vs. Negative MICs*

| | Positive MIC ($n = 115$) | Negative MIC ($n = 69$) | Significance |
|---|---|---|---|
| Range of $FET_{100\%}$ | 1.10 to 6.40 sec | 1.20 to 7.50 sec | |
| Mean $FET_{100\%} \pm 1$ SD | $3.57 \pm 1.68$ sec | $4.75 \pm 1.60$ sec | $p < 0.0001$ |
| Incidence of $FET_{100\%} < 4$ sec | $64/115 = 55.65\%$ | $21/69 = 30.43\%$ | $p < 0.0001$ |
| Incidence of $FET_{100\%} > 4$ sec | $51/115 = 44.35\%$ | $48/69 = 69.57\%$ | $p < 0.0001$ |

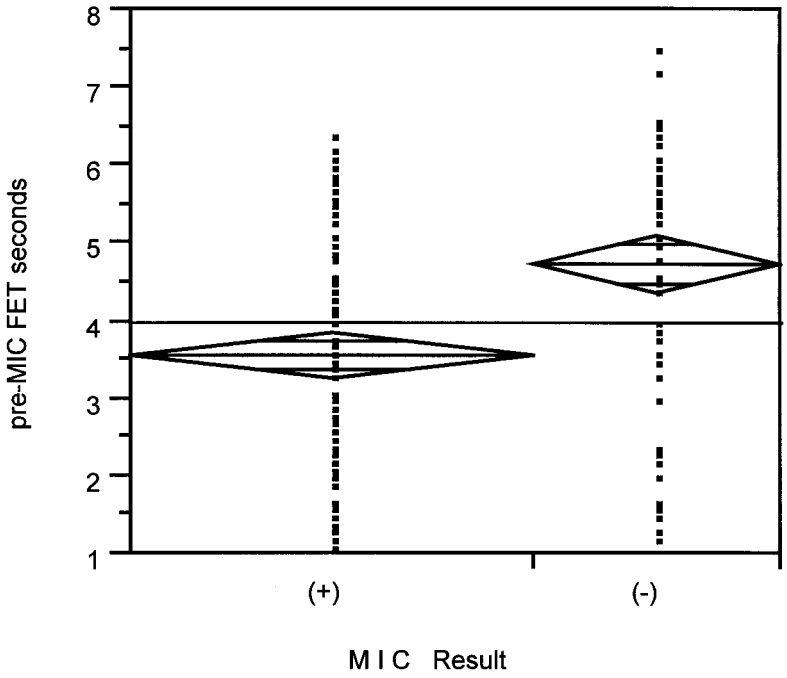


**Figure 1.** Comparison of mean pre-MIC $FET_{100\%}$ in positive vs. negative MICs. The two vertical dotted lines represent the raw pre-MIC $FET_{100\%}$ values for the respective positive and negative MIC subject groups. The horizontal line in the center of each diamond indicates the mean pre-MIC $FET_{100\%}$ for each positive vs. negative MIC group. The width of each diamond is proportional to the group sample size. Therefore, the diamond representing the group of subjects with positive MICs (115 individuals) is wider than that representing the group of subjects with negative MICs (69 individuals). The height of each diamond represents the 95% confidence interval of each sample mean.

($p < 0.001$). The incidence of positive MIC was significantly more common with $FET_{100\%} < 4$ sec (75.29%) vs. $FET_{100\%} \geq 4$ sec (51.52%) ($p < 0.001$). The mean $FET_{100\%}$ in patients with a positive MIC ($3.57 \pm 1.68$ sec) was significantly less (greater than 1 sec shorter) than the mean $FET_{100\%}$ in patients with a negative MIC ($4.73 \pm 1.60$ sec) ($p < 0.0001$) (Table 2). Furthermore, patients with $FET_{100\%} <$ 4 sec were more than 3.05 times more likely to have a positive vs. a negative MIC.

The definition of $FET_{100\%}$ is the time taken for an individual to complete a forceful exhalation after maximal inspiration (15). In general, auscultated $FET_{100\%}$ has correlated with spirometrically determined $FET_{100\%}$ (14–16). Several variables influence the performance of maximal forced expiration after maximal inspiration including airway conductance, elastic recoil of the lungs and chest wall, inspiratory muscle strength, age, and subjective factors like motivation, coaching, learning, and

fatigue (17,18). There are many discrepancies in the literature regarding cutoff values for normal vs. abnormal forced expiratory times. Published normal values for $FET_{100\%}$ have ranged from 2.18 to >6 sec (15,19–25).

Our results are contradictory to the conventionally accepted notion that expiratory time is prolonged in diseases producing airways obstruction. Previous studies in fact have reported $FET_{100\%}$ values ranging from 4.9 to 8.4 sec in patients with airways obstruction (14,20–23,25,26). Difficulties in reproducing $FET_{100\%}$ measurements have prompted concern about the efficacy of $FET_{100\%}$ measurements as a screen for small airways disease (15,16,20,26).

Consequently, it is unclear from literature reports as to what values or range of values constitute a normal or an abnormal $FET_{100\%}$. Compounding this is the ATS criteria for performance of acceptable spirometry that recommend forced expiratory time be at least 6 sec in order to obtain maximal FVC results (1). In our subset of asthmatic patients with normal $FEV_1$, FVC, $FEF_{25\%–75\%}$, and a $FET_{100\%} < 4$ sec, the maximal FVC plateau was typically achieved within the first few seconds. This is consistent with maximal forced expiratory volume–time relationships reported for normal individuals (27). Therefore, an $FET_{100\%} < 4$ sec does not necessarily lead to a submaximal FVC and cannot be explained by submaximal expiratory efforts. The reduced $FET_{100\%}$ as seen in our sample is also unlikely due to technical variability (the same technician, trained and certified under ATS standards for spirometry testing, performed all of the tests) or due to failure to comprehend on the part of the subject. Accordingly, there may be an inherent problem in satisfying the minimum 6 sec $FET_{100\%}$ ATS criteria in certain asthmatics with normal spirometry. A reduced $FET_{100\%}$ in this population should not erroneously be attributed to poor technical performance. The benchmark for an acceptable spirometry in this population may best be accomplished by establishing a maximal plateau in the volume–time curve rather than achieving a fixed time of expiration.

The pathophysiological reason for a reduced $FET_{100\%}$ in our patients with normal spirometry and a positive MIC is unclear. Small airways obstruction in these patients cannot explain the decreased $FET_{100\%}$, since the former would tend to prolong, not reduce, the terminal phase of expiration. Furthermore, the majority of our patients showed no evidence of small airways disease by $FEF_{25\%–75\%}$ and/or $FEF_{75\%}$ criteria. Prolongation of $FET_{100\%}$ in COPD is thought to reflect airway obstruction due to increased airways resistance and/or a decrease in elastic recoil pressure (28). Airway physiology is different between asthma and COPD and changes in elastic recoil and/or airways resistance are unlikely to explain a reduced $FET_{100\%}$ associated with bronchial hyperreactivity (29).

An alternative explanation of reduced $FET_{100\%}$ in our MIC positive population is that a forced expiration is an irritating maneuver in hyperreactive airways. In normal individuals, a deep inspiratory maneuver usually produces bronchodilation (30,31). In contrast, a voluntary deep inspiration results in transient bronchoconstriction in many mild to severe asthmatics (32–36). In addition, animal and human studies have shown a corresponding relationship between airways inflammation and a reduction in deep breath induced bronchodilation (36–38). Therefore, it is possible that in patients with nonspecific hyperreactivity and a reduced $FET_{100\%}$, abnormally sensitive pulmonary sensory receptors triggered during deep inspiration may terminate expiration early due to bronchoconstrictor reflexes (39,40). In addition, deep inspiration may trigger release of cytokines in patients with inflamed airways and hyperreactivity, promoting transient bronchoconstriction and early termination of a forced expiration (39,41).

## CONCLUSION

Our results suggest that patients with $FET_{100\%} < 4$ sec have an increased likelihood of having a positive MIC. While most physician offices are not equipped to perform lung volumes, conductance/resistance studies and/or diffusion studies, attention to $FET_{100\%}$ as part of standard office-based PFTs may help identify patients with normal spirometry who are likely to have a positive MIC. However, $FET_{100\%} < 4$ sec, should not substitute for MIC, but help guide diagnostic decision making. This may be of particular importance for those patients with chronic cough when other diagnostic tests like CT of the sinus and esophageal studies along with MIC need to be considered. In addition, a reduced $FET_{100\%}$ during standard spirometry should not be discarded due to poor performance.

A reduced $FET_{100\%}$ may be a marker of airway hyperreactivity, and ignoring this test result may introduce bias into test interpretations. The reason(s) for a reduced $FET_{100\%}$ in our MIC positive patients requires further investigation.

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