Methacholine-induced fall in forced vital capacity as a marker of asthma severity

J. Abisheganaden, C.-C. Chan, C. B. E. Chee and Y.-T. Wang

Department of Respiratory Medicine, Tan Tock Seng Hospital, Singapore

The dose of methacholine causing a 20% fall in forced expiratory volume in 1 sec (FEV₁) from baseline (PD₂₀) has been used as an index of asthma severity. The aim of this study was to determine if the percentage fall in forced vital capacity (FVC) from baseline at the PD₂₀ (dFVC%) is an independent marker of asthma severity.

We first retrospectively studied the dFVC% and PD₂₀ obtained from 149 consecutive newly diagnosed asthmatics with a positive methacholine-challenge test (MCT). We then performed MCT on 20 normal subjects and 35 stable asthmatics. The 'milder' asthmatics (n=20) and 'more severe' asthmatics (n=15) were on regular inhaled corticosteroids: 200 µg or less and 800 µg or more daily, respectively. A dosimeter technique was used, and normal subjects were given a cumulative dose of 2400 µg. The PD₂₀ and dFVC% were calculated using log-linear interpolation of the last two points. Student's unpaired t-tests and linear regression analyses were used for comparison and correlation of results.

There was no significant correlation between dFVC% and PD₂₀ among the 149 newly diagnosed asthmatics (r=0.1), or among the 35 known stable asthmatics (r=0.008). The more severe asthmatics had a larger dFVC% compared with the milder asthmatics (15.8% vs. 9.6%; P=0.0005). In addition, inhaled corticosteroid usage correlated better with dFVC% (r=0.56) than with PD₂₀ (r=0.36). The normal subjects had a mean fall in FVC of only 4.8%.

The percentage fall in FVC at PD₂₀ (dFVC%) may be a useful index of asthma severity which is independent of PD₂₀. This index is potentially complementary to the PD₂₀ in the assessment of asthma severity.

Introduction

Bronchial hyperresponsiveness (BHR), measured as the concentration (PC₂₀) or dose (PD₂₀) of inhaled methacholine or histamine needed to induce a 20% fall in forced expiratory volume in 1 sec (FEV₁) from baseline, is widely used as a diagnostic test for bronchial asthma as well as an index of asthma severity (1-3). However, the merits of BHR testing as an index of asthma severity have been questioned following several prospective studies which failed to show good correlation between BHR and the risk for clinical exacerbations (4-6). The PD₂₀ (or PC₂₀) is a single point in the dose-response curve which reflects the airway sensitivity to methacholine (or histamine), that is the ease of airway narrowing. The level of maximal response, which reflects the propensity for airway closure, is not obtained during routine BHR testing. This propensity for airway closure may be indicative of the risk for life-threatening exacerbations, and thus may be a more critically important index than PD₂₀. However, bronchoprovocation tests that employ high concentrations of agonist to measure the maximal plateau response directly are not practical because of the inherent risks of provoking an excessive fall in FEV₁.

Recently, Gibbons et al. (7) proposed a novel indirect method for detection of excessive bronchoconstriction in patients with mild, newly diagnosed asthma. They retrospectively measured the maximal percentage fall in forced vital capacity (FVC) at PC₂₀ (dFVC%), which reflects the gas trapped at that point of the dose-response curve due to excessive bronchoconstriction, and found that this index of airway closure was not related to the PC₂₀. However, unlike the PC₂₀, dFVC% was significantly related to the average number of prescriptions per month of oral corticosteroids, which suggested that it may be a more useful index of disease severity in asthma than PC₂₀.

This study is done in two parts with different objectives. The first part was a retrospective study of newly diagnosed asthmatics to validate Gibbons et al.’s results in our laboratory. The second part was a cross-sectional study of two different groups of stable asthmatics on inhaled corticosteroids to ascertain if dFVC% is an independent marker of disease severity.
TABLE 1. Demographic and lung function characteristics of the mild, newly diagnosed asthmatics

| Patients (n) | 149 |
| Age (years) | 32.0 ± 13.0 |
| Sex (M:F) | 78:71 |
| FEV₁ (% pred.) | 89.3 ± 14.0 |
| FVC (% pred.) | 99.7 ± 15.4 |
| Geometric standard mean PD₂₀ (μg) | 280.3 ± 1.7 |
| Geometric standard mean log PD₂₀ | 2.4 |
| % fall in FVC (dFVC%) | 13.8 ± 4.8 |

Values are expressed as means ± sd. PD₂₀ is expressed as geometric mean value with sd in doubling doses.

Methods

PART ONE

We retrospectively analysed the results of broncho-provocation testing in 578 consecutive patients referred for suspected asthma over a 1-year period between December 1995 and December 1996. Of these, 149 had a positive methacholine challenge test, technically acceptable efforts for reliable FVC measurements (at least six second efforts), and were subsequently diagnosed to have bronchial asthma based on established criteria (8). None of the subjects had taken any form of oral or inhaler bronchodilator therapy for 12 h prior to methacholine challenge testing, and all had never been on any oral corticosteroids. The demographic and lung function characteristics of these mild, newly diagnosed asthmatics are shown in Table 1.

Repeat methacholine challenge test was done randomly in nine of these patients, all of whom were non-smokers (Table 2). The average duration between the initial and repeat tests was 6 months (range 1–12 months). All were on inhaled steroids 100–1200 μg per day between the first and second tests, and there was no change in medication or steroid dosage between the two tests. The repeat tests were done to determine the stability of the PD₂₀ response and dFVC% over time in stable asthmatics.

PART TWO

In the second part of the study, we prospectively performed methacholine challenge testing on 35 outpatient stable asthmatics and 20 non-smoking, healthy subjects. Informed consent was obtained from all subjects before participation in the study. The asthmatics were divided into two groups based on disease severity prior to testing. Group 1 patients (n=20) with 'milder' asthma had symptoms less than twice per week, no nocturnal symptoms and were only on low-dose inhaled corticosteroid therapy (200 μg or less daily for 6 months) for maintenance of asthma control. Group 2 patients (n=15) with 'more severe' asthma had symptoms at least twice per week, with nocturnal symptoms on one or more nights per week, and were on regular inhaled corticosteroid 800 μg or more daily for the last 6 months. All had a baseline FEV₁ greater than 60% predicted prior to provocation tests.

METHACHOLINE CHALLENGE TESTING

The methacholine challenge tests were performed using the standard procedure described by Yan et al. (9). Aerosols of physiological saline and methacholine were generated by a dosimeter system (ME.FAR 'MB3', Bovezzo, Italy) to give an output of 0.15 ml min⁻¹ of aerosol and particle size of 0.5–4.0 μm. The time of aerosol delivery was pre-set at 1.2 s and the pause time between inhalations at 6 s. Baseline pulmonary function was first performed, followed by five inhalations of saline which acted as a diluent control. This was followed by inhalations of two different concentrations (2.5 mg ml⁻¹ and 25 mg ml⁻¹) of methacholine, to provide cumulative doses ranging from 20 to 2400 μg. Doubling doses were given within the dose range of 20–2400 μg and all subjects received the same dose range. The FEV₁

| Patients (n) | 9 |
| Mean age (years) | 39.7 ± 16.2 |
| Sex (M:F) | 3:6 |
| FEV₁ (l) | First test 2.48 ± 0.97, Second test 2.42 ± 0.77, P value* 0.89 |
| FVC (l) | 3.01 ± 1.04, 3.1 ± 0.93, 0.85 |
| FEV₁ FVC⁻¹ | 0.82 ± 0.12, 0.78 ± 0.10, 0.48 |
| GSM PD₂₀ (μg) | 140.6 ± 1.0, 164.1 ± 1.2, 0.48 |
| GSM log PD₂₀ | 2.11 ± 0.45, 2.17 ± 0.45, 0.75 |
| dFVC% | 12.8 ± 5.0, 11.9 ± 4.8, 0.66 |

GSM, geometric standard mean; PD₂₀, dose of methacholine needed to induce a 20% fall in FEV₁; dFVC%, percentage fall in FVC at PD₂₀.

Values are expressed as mean ± sd. PD₂₀ is expressed as geometric mean value with sd in doubling doses.

*Not statistically significant.
and FVC were recorded by a pneumotachograph system (Sensormedics 2450, Yorba Linda, CA, U.S.A.) 1 min after each dose of methacholine. Spirometric measurements were made in accordance with the recommendations of the American Thoracic Society (10). The time course of the preceding inspiration was standardized (11) with rapid maximal inspiration without end-inspiratory pause, and the FVC manoeuvre was continued until a plateau in the forced expiratory volume curve was obvious by visual inspection. The minimum duration of the FVC manoeuvre was 6 sec. Methacholine challenge was stopped when either FEV₁ fell by at least 20% or more from baseline measured after saline inhalation, or until the maximum dose (2400 μg) of methacholine was reached if the former was not achieved. The PD₂₀ was obtained from the log dose-response curve by linear interpolation of the last two points. The percentage fall in FVC at the PD₂₀ dose (dFVC%) of methacholine relative to the baseline FVC after saline inhalation was also calculated using log-linear interpolation.

STATISTICAL ANALYSIS

The values of FEV₁ and FVC were expressed as percentages of predicted based on data from our local population (12). Summary values were expressed as mean (±SD) except for PD₂₀ which was expressed as geometric standard mean (GSM) value with SD in doubling doses. Comparisons between two groups of patients were made using the Student’s two-tailed unpaired t-test. Correlations between pulmonary function measurements were made using linear regression analysis. A P-value of 0.05 or less was taken to be significant. The method of Bland and Altman (13) was used to assess repeatability of PD₂₀ and dFVC%.

Results

PART ONE

Bronchoprovocation results of the nine asthmatics who underwent repeat methacholine challenge testing showed that the average difference in PD₂₀ between the two tests was less than one doubling dose (0.57 doubling dose) and was not statistically significant (t = -0.75, P = 0.48). Similarly, there was no statistically significant difference between dFVC% measured during the first vs. the second tests (t = -0.46, P = 0.69). The measurements of dFVC% and PD₂₀ made approximately 6 months apart in these nine patients are presented in Fig. 1(a) and (b). There was no significant relationship found between the difference in PD₂₀ and the difference in dFVC% between the two tests (r = 0.22, P = 0.57). The coefficient of repeatability for PD₂₀ and dFVC%, respectively, were 317 μg methacholine and 11% fall in FVC (13).

The demographic characteristics and mean lung function data of the 149 patients are summarized in Table 1 and the frequency distribution of the dFVC% for the same patients is shown in Fig. 2. The dFVC% had a normal frequency distribution (Kolmogorov-Smirnov one-sample test of normality, P = 0.17).

Figure 3 shows the plot of the dFVC% against the PD₂₀ for the 149 patients. As shown in the Figure, these patients showed a broad range of response in the fall in FVC to methacholine (1–25%). There was no significant linear correlation between dFVC% and PD₂₀ (r = 0.1, P = 0.1). This result is very similar to those obtained by Gibbons et al. (7).
PART TWO

The patients in Group 1 had a significantly higher baseline FEV₁ (% pred.) than the patients in Group 2 (P=0.016) (Table 3). Both groups of patients had similar age and sex ratios. Group 1 patients had a significantly higher PD₂₀ and lower dFVC% than patients in Group 2 (Table 3). Overall, for the combined data (Groups 1 and 2), there was no significant correlation between dFVC% and PD₂₀ measurements (r=0.008, P=0.97). There was no significant correlation between baseline pulmonary function (FEV₁, % pred.) and BHR (PD₂₀) (r=0.15, P=0.07). Inhaled steroid usage correlated better with dFVC% (r=0.56, P=0.005) than with PD₂₀ (r=0.36, P=0.03).

The healthy, non-smoking subjects were of average age 32.4 (±9.3) years, and consisted of nine women and 11 men. The average fall in FVC and FEV₁ were 4.8 (±3.6)% and 7.7 (±3.5)% respectively. There was a fall in FVC of more than 10% in only two subjects (12.3 and 11.9%). There was no significant relationship between percentage fall in FEV₁ and FVC (r=0.05, P>0.1). There was still no significant relationship even after removing the two subjects with percentage fall in FVC >10% (r=0.3, P>0.1). The mean values of the fall in FVC either at 2400 µg methacholine (normal subjects) (±SD) are shown in Fig. 4.

**Discussion**

In asthmatics, the propensity for airway closure may be indicative of the risk of life-threatening exacerbations, and thus may be more critically important than the PD₂₀, which reflects mainly the ease of airway narrowing. Indeed, several prospective studies have found poor correlation between PD₂₀ and the risk of disease exacerbation (4,5).

**TABLE 3.** Comparison of demographic, baseline spirometry and methacholine provocation data between two groups of stable asthmatics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (milder asthmatics)</th>
<th>Group 2 (more severe asthmatics)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.4 (11)</td>
<td>37.8 (15)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/10</td>
<td>8/7</td>
<td>—</td>
</tr>
<tr>
<td>Inhaled steroids day⁻¹ (µg)</td>
<td>170 (47)</td>
<td>1040 (238.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline FEV₁ (% pred.)</td>
<td>96.4 (11.7)</td>
<td>84.7 (15.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Baseline FVC (% pred.)</td>
<td>102.1 (15.7)</td>
<td>104.9 (15.1)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>GSM PD₂₀ (µg)</td>
<td>466.5 (1.4)</td>
<td>106.2 (1.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>dFVC%</td>
<td>9.6 (4.2)</td>
<td>15.8 (5.4)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Values are expressed as mean (sd). PD₂₀ is expressed as geometric-standard mean (GSM) value with sd in doubling doses. PD₂₀, dose of methacholine needed to induce a 20% fall in FEV₁; dFVC%, maximal % fall in FVC at PD₂₀.
The maximal response plateau on the methacholine–FEV\textsubscript{1} dose-response curve reflects the extent to which the airways can narrow, when being exposed to high doses of inhaled methacholine. It is a more direct indicator of the degree of protection against excessive airway narrowing (14–18). However, it is neither safe nor easy to do in asthmatics.

It has long been appreciated that residual volume (RV) increases (19–21) and vital capacity (VC) falls (22) significantly in asthmatics during induced bronchoconstriction. Indeed, hyperinflation and air trapping with increased total lung capacity (TLC) and RV from excessive bronchoconstriction is a feature of severe asthma and status asthmaticus (23–25). However, during BHR testing, the TLC remains unchanged (26). In the susceptible asthmatic, the gas trapping induced during BHR testing should increase in a dose-dependent manner resulting in a dose-dependent rise in the RV. In practice, this should be easily measurable as a dose-dependent fall in the FVC (7). Moreover, the FEV\textsubscript{1} is predominantly an index of large airways obstruction and is not dependent on the site of the flow limiting segment, which changes towards the periphery in the case of pressure loss over the peripheral airways or at low elastic recoil pressure. The dFVC\% might be a more direct index of small airways obstruction or closure for low lung volumes.

In the first part of this study, we have duplicated Gibbons et al.'s (7) findings on the percentage fall in FVC at PD\textsubscript{20} (dFVC\%) in mild, newly diagnosed asthmatics. It is an index of gas-trapping not related to PD\textsubscript{20}. In addition, in the second part of the study, we found similar findings in stable asthmatics on inhaled corticosteroids. We found that dFVC\% was significantly higher in the group with more severe disease. Moreover, the inhaled steroid usage in stable asthmatics correlated better with dFVC\% than with PD\textsubscript{20}. The dFVC\% may therefore provide information regarding excessive airway narrowing in stable asthmatics. This method of assessing propensity for airway closure, viz dFVC\%, can be safely and conveniently measured during routine BHR testing in both mild, newly diagnosed asthmatics and stable asthmatics on inhaled steroids. This approach carries no additional risk over that of a routine bronchial challenge test and avoids the problems inherent in provoking an excessive fall in FEV\textsubscript{1}.

We found that our asthmatic patients had a broad range of responses in their FEV\textsubscript{1} and FVC to methacholine, suggesting wide variability in the degree of protection against excessive bronchoconstriction in the asthmatic population. Among the 149 consecutive mildly, newly diagnosed asthmatics, there was no significant correlation between the dFVC\% and the PD\textsubscript{20} (r=0-14, P=0-1). There was also no significant correlation between the dFVC\% and the PD\textsubscript{20} (r=0-008, P=0-97) among the 35 stable asthmatics on inhaled corticosteroids. These findings imply that the ease of bronchoconstriction, as measured by PD\textsubscript{20} and the degree of gas trapping or propensity for airway closure, as reflected by dFVC\%, might be due to different mechanisms (18,27,28) and may represent independent responses of the airways to pharmacological provocation. While the fall in FEV\textsubscript{1} reflects the tone in the large airways, the fall in FVC may be a more relevant indicator of the peripheral airway pathological process that leads to the asthmatic attack.

There was a normal frequency distribution in the percentage fall in FVC at the PD\textsubscript{20} dose among the 149 consecutive cases, with a mean fall in FVC from baseline of 13.8 (± 4.8)%. Our findings are very similar to that by Gibbons et al. (7), who documented a mean fall of 13.2 (± 5.5)% among 146 asthmatics.

Reproducibility studies performed approximately 6 months apart demonstrated stability of patterns of response of PD\textsubscript{20} and dFVC\% over time. The difference in PD\textsubscript{20} responses between the first and second tests was less than one doubling dose of methacholine and was not statistically significant.

An important new finding of this study was that the dFVC\% was able to distinguish mild asthmatics from those who had more severe disease. The patients in Group 2 had more severe asthma as evidenced by increased symptoms, lower baseline FEV\textsubscript{1}, lower PD\textsubscript{20}, and higher daily inhaled corticosteroid requirement. They showed greater falls in FVC with methacholine. Moreover, inhaled corticosteroid usage correlated better with dFVC\% (r=0.56) than with PD\textsubscript{20} (r=0.36). This new finding may have potential clinical application as a marker to identify the stable asthmatic at risk for serious exacerbations. The dFVC\% may be an indirect reflection of the severity of airway inflammation, and thus identify the asthmatic who would require a higher dose of corticosteroid therapy and closer monitoring. An alternative possibility is that it is also a reflection of the degree of overall chronic cellular and remodelling components, or other more permanent changes in the airways.

Methacholine challenge testing in the normal subjects revealed a mean fall in FVC of only 4.8% from baseline after inhaling a cumulative dose of 2400 \( \mu \text{g} \) of methacholine. This information gave us an objective estimate of the magnitude of fall in normal subjects using our pulmonary function testing protocol, which was important in deciding what was a significant fall in FVC when using the protocol.

In summary, we have shown that excessive airway narrowing as measured by the fall in FVC measured at the PD\textsubscript{20} dose of inhaled agonist may be measured conveniently and safely during routine BHR testing in asthmatic patients. The dFVC\% and PD\textsubscript{20} were not correlated among newly diagnosed asthmatics, and also were not correlated in a cross-sectional study of stable mild to moderate asthmatics. They may represent independent responses of the airways to pharmacological provocation. We conclude that the percentage fall in FVC at PD\textsubscript{20} (dFVC\%) has potential as a clinically useful measurement in asthmatics. It showed a much stronger correlation with inhaled steroid usage when compared to the PD\textsubscript{20}, and was able to distinguish mild from more severe disease in stable asthmatics. This index of propensity for airway closure may be a useful physiological marker in identifying the asthmatic at risk for serious disease.

References

1. Murray AB, Fergusson AC, Morrison B. Airway responsiveness to histamine as a test of overall severity


