A comparison of three measures of the response to inhaled methacholine

A.J. Knox, H.E. Coleman, J.R. Britton, A.E. Tattersfield

ABSTRACT: In studies of asthma prevalence bronchial responsiveness has usually been measured as the provocative dose of bronchoconstrictor causing a 20% fall in FEV \(_1\) (PD\(_{20}\)FEV\(_1\)). This is a relatively insensitive index of bronchial reactivity. In some asthma subjects and can conversely reduce the magnitude in induced bronchoconstriction in other asthmatic and normal subjects [7-13]. However, for this method to be useful, it must also be repeatable. Dhaub et al., using the method of Cockcroft et al. [14], found that flow at 40% vital capacity (PC\(_{40}\)V\(_{30}\)) taken from a partial flow volume manoeuvre was more sensitive than PD\(_{20}\)FEV\(_1\) but slightly less repeatable. The aim of the present study was to try to determine whether it was possible to increase the sensitivity without loss of repeatability using the method of Yan et al. [15] for the challenge since this is used most widely for epidemiological studies. We compared the repeatability and sensitivity of PD\(_{20}\)FEV\(_1\), PD\(_{10}\)FEV\(_1\), and PD\(_{20}\)V\(_{30}\) (provocative dose of histamine causing a 40% reduction in V\(_{30}\)) in twenty asthmatic subjects.

Methods

Subjects

Twenty asthmatic subjects (11 male) aged 19–66 years
were studied. To be included, all subjects had to have an \( \text{FEV}_1 > 60\% \) predicted, an improvement in \( \text{FEV}_1 > 15\% \) after 200 \( \mu \)g inhaled salbutamol, a \( \text{PD}_{40} \text{FEV}_1 < 4 \) \( \mu \)mol histamine, and to be clinically stable on inhaled therapy only. Thirteen subjects were taking inhaled corticosteroids, and all were taking inhaled beta agonists which were withheld 6 hours prior to the commencement of each measurement (table 1). Sixteen subjects were atopic. Nine of the 20 subjects who entered the study had prior experience of challenge test procedures. Written consent was obtained from all subjects. The study was approved by the Nottingham City Hospital Ethics Committee.

Table 1. – Baseline subject characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>42</td>
<td>19–66</td>
</tr>
<tr>
<td>Height cm</td>
<td>168</td>
<td>152–191</td>
</tr>
<tr>
<td>Duration of asthma yrs</td>
<td>15</td>
<td>1–50</td>
</tr>
<tr>
<td>( \text{FEV}_1 ) l</td>
<td>2.6</td>
<td>1.4–5.2</td>
</tr>
<tr>
<td>( \text{FVC} ) l</td>
<td>3.9</td>
<td>2.0–7.2</td>
</tr>
<tr>
<td>( \text{FEV}_1/\text{FVC} ) %</td>
<td>68</td>
<td>44–91</td>
</tr>
</tbody>
</table>

Experimental procedure

\( \text{FEV}_1 \) was measured on a dry bellows spirometer (Vitalograph\textsuperscript{®}) taking the higher of two measurements within 100 ml. Flow at 30\% of vital capacity (\( \text{V}_{30} \)P) was measured on a rolling seal spirometer (Ohio) with subjects performing a forced expiration from approximately 50\% of vital capacity to residual volume followed by inspiration to total lung capacity and a forced expiration to residual volume. Values of \( \text{V}_{30} \)P were calculated by a microprocessor attached to the spirometer. The mean of two technically correct procedures was used in all calculations. The initial forced vital capacity was used to determine the lung volume 70\% below total lung capacity from which all subsequent \( \text{V}_{30} \)P measurements were determined as recommended by PRIDE [16].

Protocol

Subjects attended the laboratory on four days at the same time of day. The tests were performed at least one and not more than seven days apart in random order. After resting for 15 minutes, baseline \( \text{FEV}_1 \) was measured. Subjects then performed a methacholine challenge test using a modification of the method of YAN et al. [15], using DeVilbiss hand held nebulisers with an output ranging from 2.5–3.5 \( \mu \)l per activation. After baseline measurement, subjects inhaled 3 puffs of saline followed by cumulative doses of methacholine over the dose range 0.048–24.5 \( \mu \)mol. The airway response was measured one minute after each dose of methacholine. On two occasions response was measured as \( \text{FEV}_1 \), and on two occasions as \( \text{V}_{30} \)P. The test was continued until \( \text{FEV}_1 \) had fallen by 20\% or \( \text{V}_{30} \)P had fallen by 40\% from the post-saline values. \( \text{PD}_{10} \text{FEV}_1 \), \( \text{PD}_{20} \text{FEV}_1 \), and \( \text{PD}_{40} \text{V}_{30} \)P values were calculated by interpolation on log dose response plots.

Statistical analysis

Baseline values of \( \text{FEV}_1 \) on the four study days were compared by analysis of variance (ANOVA). Log transformed PD values were used in all analyses. Student’s paired t-tests were performed on the two \( \text{PD}_{20} \) and two \( \text{PD}_{40} \) values to look for any other effect. Differences in sensitivity were assessed by two way ANOVA on the mean logPD\textsubscript{10} \( \text{PD}_{20} \), and \( \text{PD}_{40} \) values for each subject. The standard deviations of the differences between the two values of \( \text{PD}_{20} \text{FEV}_1 \), \( \text{PD}_{10} \text{FEV}_1 \), and \( \text{PD}_{40} \text{V}_{30} \)P were calculated with in subject deviation of these estimates was calculated by dividing the standard deviation by the square root of two [17]. This was used to construct 95\% ranges for a single measurement by each method (formula: 95\% range= \text{PD}_{10} \times \text{within subject sd}).

The intraclass correlation co-efficient, a dimensionless measure of repeatability, was calculated for each method by dividing the between subject variance by the total variance in a one way ANOVA [18].

Results

One subject was unable to perform the partial flow manoeuvre satisfactorily and had to be withdrawn. The remaining subjects all had a measurable PD value in all tests. When asked, all 20 subjects found the \( \text{PD}_{20} \text{FEV}_1 \) manoeuvre easier to perform.

Table 2. – Measures of repeatability for the three methods

<table>
<thead>
<tr>
<th></th>
<th>( \text{PD}_{10} \text{FEV}_1 )</th>
<th>( \text{PD}_{20} \text{FEV}_1 )</th>
<th>( \text{PD}<em>{40} \text{V}</em>{30} )P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diff between 1st and 2nd test (log\textsubscript{10} units) mean</td>
<td>0.1</td>
<td>-0.014</td>
<td>-0.012</td>
</tr>
<tr>
<td></td>
<td>( \text{sd} )</td>
<td>0.48</td>
<td>0.41</td>
</tr>
<tr>
<td>Within subject ( \text{sd} ) (log\textsubscript{10} units)</td>
<td>0.34</td>
<td>0.29</td>
<td>0.29</td>
</tr>
<tr>
<td>95% range for a single measurement (doubling doses)</td>
<td>2.35</td>
<td>2.02</td>
<td>2.02</td>
</tr>
<tr>
<td>Intraclass correlation coefficient</td>
<td>0.63</td>
<td>0.79</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Table 3 - Geometric mean PD values for the three methods

<table>
<thead>
<tr>
<th>Method</th>
<th>1st reading</th>
<th>2nd reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD_{20}FEV_1</td>
<td>0.36 (1.95)</td>
<td>0.28 (1.76)</td>
</tr>
<tr>
<td>PD_{20}FEV_1</td>
<td>0.67 (2.18)</td>
<td>0.65 (1.97)</td>
</tr>
<tr>
<td>PD_{40}V_{30}P</td>
<td>0.24 (1.66)</td>
<td>0.23 (1.79)</td>
</tr>
</tbody>
</table>

Values are geometric mean (SD in doubling doses)

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**Discussion**

We found no difference in repeatability between PD_{20}FEV_1 and PD_{20}V_{30}P, the 95% range for a single measurement being equal at 2.02 doubling doses of methacholine. The equal repeatability of these tests probably reflects the fact that although FEV_1 has been shown to be a more repeatable measurement than flow at low lung volumes taken from flow volume curves [19, 20], the PD_{40}V_{30}P is measured on a steeper part of the dose response slope than PD_{20}FEV_1. PD_{10}FEV_1 was slightly less repeatable with a 95% range of 2.35 doubling doses. The repeatability of PD_{10} and PD_{20}FEV_1 in our study are very similar to that found by CHINN et al. [6] in a community population using the Yan method.

The only previous study which has compared the repeatability of PD_{20}FEV_1 and of flow at low lung volumes is a study by DEHAUT et al. [9], in which histamine was given by the method of COCKROFT et al. [14], and flow at 40% of vital capacity (PC_{40}V_{30}P) was compared. They found that PC_{40}V_{30}P was less repeatable than PC_{20}FEV_1, the 95% ranges for a single estimate being 1.83 and 1.59 respectively. The slightly better repeatability of PC_{20}FEV_1 in Dehaut's study compared to ours is unlikely to be due to differences in methods, as the only study to compare the Cockcroft with the Yan method directly showed the repeatability of the Yan technique to be marginally better [21]. Measurement of repeatability depends on within subject variation in airway calibre and on the repeatability of the technique, and there is no easy way to separate the two. The difference in repeatability between Dehaut's study and ours may be due to differences in subjects. Dehaut et al. do not mention the previous experience of their subjects, but only nine of our subjects had previous experience of challenge test procedures. The fact that the previous experience of these nine was with PD_{20}FEV_1 would tend to bias repeatability
towards $PD_{20}/FEV_1$, and the same may have been true in Dehaut's study.

Flow at low lung volumes has been shown to be more sensitive than $PD_{20}/FEV_1$ in several studies [8-13]. In our study, $PD_{V_{150}}$ was more sensitive than both $PD_{V_{30}}$ or $PD_{20}/FEV_1$, by 1.48 and 0.35 doubling doses respectively. In population studies this would be likely to increase the number of responders by approximately twofold, if the maximum dose of methacholine used was 25 μmol as in the present study.

We used the intraclass correlation co-efficient as a dimensionless index of repeatability. This measure gives the proportion of the total variance which can be accounted for by between subject differences, and therefore indicates how good a test is at discriminating between subjects. The intraclass correlation co-efficient for $PD_{V_{150}}$ was 0.69 compared with 0.79 for $PD_{20}/FEV_1$, suggesting that the increased sensitivity of $PD_{V_{150}}$ is achieved with some loss of discrimination of between subject differences. The intraclass correlation for $PD_{20}/FEV_1$ was the lowest at 0.63, suggesting that this measure is least able to detect between subject differences.

Other factors must be taken into account when considering the use of partial flow volume manoeuvres for epidemiological studies. The time taken to obtain $PD_{V_{150}}$ was similar to that taken for $PD_{20}/FEV_1$ measurements (usually 10 to 15 minutes). One subject, however, was unable to perform the partial manoeuvre satisfactorily, and, when asked, all subjects thought that the partial manoeuvre was more difficult to perform. Another drawback is that the equipment required is generally less portable than a bellows spirometer. This problem is likely to be overcome with the introduction of more portable computerized equipment for recording expiratory flow volume loops.

The use of flow at low lung volumes taken from partial flow volume curves may prove a useful technique to assess bronchoconstriction in future studies of asthma prevalence in the community. This would need to be tested in a randomly selected community population and more portable equipment would be needed.

Acknowledgements: We thank Mrs S. Cooper for help with subject recruitment.

References

dose provocatrice d'une chute de 10% du VEMS (PD_{10} VEMS) n'ont pas prouvé qu'elles soient globalement advantageuses en raison d'une plus faible reproductibilité. On a suggéré que la mesure de la réactivité bronchique par l'étude des débits à petit volume pulmonaire, mesuré à partir d'une courbe débit-volume partielle, pourrait être un indice plus sensible de la broncho-constriction que la PD_{20} VEMS. Si elle était aussi reproductible, elle aurait des avantages dans la pratique épidémiologique. Chez 20 sujets atteints d'asthme, nous avons comparé la sensibilité et la reproductibilité de PD_{10} VEMS, PD_{20} VEMS et de la dose provocatrice, provoquant une chute de 40% du débit à 30% de la capacité vitale (PD_{40} VT_{30} P), après une provocation à la méthacholine. PD_{40} VT_{30} P est plus sensible que les deux autres mesures (PD_{10} VEMS et PD_{20} VEMS de 1.48 et 0.35, doses de doublement de la méthacholine, respectivement. PD_{20} VEMS et PD_{40} VT_{30} P ont une reproductibilité égale, la marge à 95% pour une estimation isolée des deux étant de 2.02 DD. PD_{20} VEMS est moins reproductible avec une marge à 95% de 2.35 DD. Les valeurs du coefficient de corrélation intra-classe qui mesurent la capacité d'un test de discrimination entre sujets étaient respectivement de 0.63, 0.79 et 0.69 pour PD_{10} VEMS, PD_{20} VEMS et PD_{40} VT_{30} P. La mesure de la réactivité bronchique par PD_{40} VT_{30} P semble une méthode utile pour les études de la prévalence de l'asthme, en raison d'une sensibilité accrue et d'une reproductibilité similaire. Eur Respir J., 1989, 2, 736-740