Mid-expiratory flow versus FEV\textsubscript{1} measurements in the diagnosis of exercise induced asthma in elite athletes

J W Dickinson, G P Whyte, A K McConnell, A M Nevill, M G Harries

Background: A fall in FEV\textsubscript{1} of $\geq 10\%$ following bronchoprovocation (eucapnic voluntary hyperventilation (EVH) or exercise) is regarded as the gold standard criterion for diagnosing exercise induced asthma (EIA) in athletes. Previous studies have suggested that mid-expiratory flow (FEF\textsubscript{50}) might be used to supplement FEV\textsubscript{1} to improve the sensitivity and specificity of the diagnosis. A study was undertaken to investigate the response of FEF\textsubscript{50} following EVH or exercise challenges in elite athletes as an adjunct to FEV\textsubscript{1}.

Methods: Sixty male (36 asthmatic, 30 non-asthmatic) and 50 female (24 asthmatic, 26 non-asthmatic) elite athletes volunteered for the study. Maximal voluntary flow-volume loops were measured before and 3, 5, 10, and 15 minutes after stopping EVH or exercise. A fall in FEV\textsubscript{1} of $\geq 10\%$ and a fall in FEF\textsubscript{50} of $\geq 26\%$ were used as the cut off criteria for identification of EIA.

Results: There was a strong correlation between $\Delta$FEV\textsubscript{1} and $\Delta$FEF\textsubscript{50} following bronchoprovocation ($r = 0.94, p = 0.000$). Sixty athletes had a fall in FEV\textsubscript{1} of $\geq 10\%$ leading to the diagnosis of EIA. Using the FEF\textsubscript{50} criterion alone led to 21 (35\%) of these asthmatic athletes receiving a false negative diagnosis. The lowest fall in FEF\textsubscript{50} in an athlete with a $\geq 10\%$ fall in FEV\textsubscript{1} was 14.3\%. Reducing the FEF\textsubscript{50} criteria to $\geq 14\%$ led to 13 athletes receiving a false positive diagnosis. Only one athlete had a fall in FEF\textsubscript{50} of $\geq 26\%$ in the absence of a fall in FEV\textsubscript{1} of $\geq 10\%$ ($\Delta$FEV\textsubscript{1} = 8.9\%).

Conclusion: The inclusion of FEF\textsubscript{50} in the diagnosis of EIA in elite athletes reduces the sensitivity and does not enhance the sensitivity or specificity of the diagnosis. The use of FEF\textsubscript{50} alone is insufficiently sensitive to diagnose EIA reliably in elite athletes.

Exercise induced asthma (EIA) occurs in approximately 90\% of chronic asthmatics\textsuperscript{1} and has previously been reported to occur in 7–50\% of athletic individuals.\textsuperscript{2–4} Asthmatic elite athletes currently require evidence of asthma to obtain a therapeutic use exemption certificate which enables them to use therapeutic doses of inhaled $\beta_{2}$ agonists in and out of competition.\textsuperscript{5} EIA has previously been diagnosed by a number of challenge methods including exercise,\textsuperscript{6–8} eucapnic voluntary hyperventilation (EVH),\textsuperscript{9–11} methacholine,\textsuperscript{12, 13} histamine,\textsuperscript{14} saline,\textsuperscript{15} and mannitol.\textsuperscript{16, 17} The International Olympic Committee’s Medical Commission (IOC-MC) considers positive tests from exercise, EVH, saline, histamine, and methacholine challenges as evidence of EIA. Methacholine and histamine, however, have been shown to be less specific than exercise for EIA diagnosis.\textsuperscript{18–19} Exercise and EVH challenges are regarded as the most specific methods of diagnosing EIA in elite athletes.\textsuperscript{11}

In all EIA tests recognised by the IOC-MC, forced expiratory volume in 1 second (FEV\textsubscript{1}) is the parameter by which changes in maximal expiratory function are assessed, but no “gold standard” methodology exists for athletes or non-athletes.\textsuperscript{20} Previous studies that have used FEV\textsubscript{1} to diagnose EIA have suggested using falls in FEV\textsubscript{1} ranging from 7\% to 20\% as cut off criteria.\textsuperscript{21–23} The work carried out by Custovic et al\textsuperscript{24} therefore provides promising evidence to support the addition of mid expiratory flow rates to FEV\textsubscript{1} in the diagnosis of EIA in children that might also be applied to elite athletes. FEF\textsubscript{50} and FEF\textsubscript{25–75} measurements are highly correlated and the correlation of the two is reasonably constant. Based on this finding, Bar-Yishay et al\textsuperscript{25} suggested that reporting both measurements is unnecessary, and they suggested that FEF\textsubscript{50} should be the preferred measure. This preference was based on the argument that FEF\textsubscript{50} is easily and directly determined while FEF\textsubscript{25–75} is a calculated value.

Abbreviations: EIA, exercise induced asthma; EVH, eucapnic voluntary hyperventilation; FEF\textsubscript{50}, forced expiratory flow at 50\% of vital capacity; FEV\textsubscript{1}, forced expiratory volume in 1 second; FVC, forced vital capacity.
voluntary ventilation (30 of hyperventilating for 6 minutes at a rate of 85% maximal athletes following a bronchoprovocation challenge. During the EVH challenge was a medical gas containing 21% in a sport-specific environment. 30 EVH challenges consisted.

The lowest values of FEV1 and FEF50 following either exercise or EVH were recorded and the change was calculated (Δ). A ΔFEV1 of ≥-10% and a fall in FEF50 of ≥26% were considered cut off criteria for EIA diagnosis.24

RESULTS
There was a strong positive correlation between ΔFEV1 and ΔFEF50 following bronchoprovocation (r = 0.94, p = 0.000). Sixty athletes (52%) had a ΔFEV1 fall of ≥10% leading to the diagnosis of EIA (fig 1). Using the FEF50 criteria alone led to 21 (35%) asthmatic athletes receiving a false negative diagnosis; thus, 39 athletes met both FEV1 and FEF50 criteria. The lowest fall in ΔFEV1 in an athlete with a FEV1 of <26% were considered cut off criteria for EIA diagnosis.

METHODS
Following ethical approval from Harrow local research ethics committee, 66 male elite summer and winter athletes of mean (SD) age 25.1 (4.9) years, height 180.7 (7.8) cm, body mass 77.3 (12.5) kg and 50 female elite athletes of mean (SD) age 24.3 (5.4) years, height 168.2 (7.9) cm, and body mass 62.6 (9.9) kg who held either a Gold or Silver British Olympic Association passport (indicating current or potential Olympic competitive standard) provided written informed consent and volunteered for the study. Of the athletes who participated in this study, 83 had a previous diagnosis of EIA and where using asthma medication. The other 33 athletes had reported symptoms of EIA to a sports physician who had referred them to be tested for EIA. The testing took place at the Olympic Medical Institute, Harrow between June 2003 and June 2004. Athletes were tested at least 2 weeks after a respiratory infection and at least 12 hours following a training session. Each athlete completed either an exercise or EVH challenge. Exercise challenges involved exercising at an intensity of >85% of maximal heart rate for 6–10 minutes in a sport-specific environment.26 EVH challenges consisted of hyperventilating for 6 minutes at a rate of 85% maximal voluntary ventilation (30 × baseline FEV1). The gas inspired during the EVH challenge was a medical gas containing 21% O2, 5% CO2 and 74% N2.21 For both exercise and EVH challenges, maximal flow-volume loops were measured before and at 3, 5, 10 and 15 minutes after stopping exercise or EVH using a digital spirometer (MicroLab ML3500, Micro Medical Ltd, Rochester, UK) which met ATS guidelines. The lowest values of FEV1 and FEF50 following either exercise or EVH were recorded and the change was calculated (Δ). A ΔFEV1 of ≥-10% and a fall in FEF50 of ≥26% were considered cut off criteria for EIA diagnosis.

Figure 1 Delta FEV1 versus delta FEF50.

![Figure 1](https://example.com/figure1.png)

Table 1 Mean (SD) changes in FEF50 and FVC following bronchoprovocation challenge

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>PFE</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEF50 (l/s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmatic</td>
<td>3.86 (0.92)</td>
<td>2.39 (0.84)**</td>
<td>4.99 (1.00)</td>
<td>4.45 (1.16)**</td>
<td></td>
</tr>
<tr>
<td>Non-asthmatic</td>
<td>4.79 (1.37)</td>
<td>4.43 (1.31)</td>
<td>4.81 (1.03)</td>
<td>4.65 (1.04)</td>
<td></td>
</tr>
</tbody>
</table>

**Significantly different (p<0.05) from pre-test value.

Table 2 True and false positive and negative diagnoses based on FEF50 cut off value of 26%

<table>
<thead>
<tr>
<th></th>
<th>True positive</th>
<th>True negative</th>
<th>Total true</th>
<th>False negative</th>
<th>False positive</th>
<th>Total false</th>
<th>Total true</th>
<th>Total with EIA</th>
<th>Total without EIA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>39</td>
<td>55</td>
<td>94</td>
<td>21</td>
<td>1</td>
<td>22</td>
<td>116</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative</td>
<td>24</td>
<td>34</td>
<td>58</td>
<td>20</td>
<td>1</td>
<td>21</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>89</td>
<td>152</td>
<td>41</td>
<td>2</td>
<td>43</td>
<td>179</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 True and false positive and negative diagnoses based on FEF50 cut off value of 14%

<table>
<thead>
<tr>
<th></th>
<th>True positive</th>
<th>True negative</th>
<th>Total true</th>
<th>False negative</th>
<th>False positive</th>
<th>Total false</th>
<th>Total true</th>
<th>Total with EIA</th>
<th>Total without EIA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>51</td>
<td>43</td>
<td>94</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>101</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>False negative</td>
<td>13</td>
<td>27</td>
<td>40</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>50</td>
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<tr>
<td>Total</td>
<td>64</td>
<td>70</td>
<td>134</td>
<td>18</td>
<td>2</td>
<td>20</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ΔFEV1 = \( y = 1.3805x - 4.6986 \)
failed to develop EIA (ΔFEV₁ < 10%) following bronchoprovocation challenge. Of the 33 athletes who had been referred for testing but had no previous diagnosis of EIA, 10 athletes presented with EIA following bronchoprovocation.

The values for FEF₅₀ and forced vital capacity (FVC) before and after bronchoprovocation challenge are shown in table 1. FEF₅₀ (p = 0.000) and FVC (p = 0.000) were significantly lower after bronchoprovocation in the asthmatic athletes. There was no significant change in FEF₅₀ or FVC before and after bronchoprovocation challenge in athletes who did not have a fall in FEV₁ of ≥10%.

The specificity, sensitivity, predictive value of positive test and efficiency of FEF₅₀ cut off criteria of 26% and 14% are shown in tables 2, 3 and 4, respectively.

DISCUSSION

This study shows that the addition of FEF₅₀ reduces the sensitivity of EIA diagnosis following exercise or EVH challenge. Of the 60 athletes who were diagnosed with EIA using IOC-MC criteria of a ≥10% fall in FEV₁, 21 (35%) would have received a false negative diagnosis using a combination of FEV₁ and FEF₅₀ falls. Furthermore, only one athlete exceeded the criterion for FEF₅₀ but not for FEV₁. Our study therefore suggests that FEF₅₀ does not improve the diagnosis of EIA in elite athletes using the IOC-MC criteria.

In previous studies, measurements of FEF₂₅₋₇₅ have been used to supplement FEV₁ in the diagnosis of EIA in children and athletes. Fonseca-Guedes et al noted that FEF₂₅₋₇₅ is a more sensitive measure of obstruction in the small airways than FEV₁. Thus, EIA may be a disease that consistently affects the expiratory flow through the small airways. Fonseca-Guedes et al noted that FEF₂₅₋₇₅ is a more sensitive measure of obstruction in the small airways than FEV₁. Thus, EIA may be a disease that consistently affects the expiratory flow through the small airways.

A number of studies have examined the diagnosis of EIA in athletes but they have not specifically used mid-expiratory flow rates as a criterion for making the diagnosis. Rundell et al suggested that a fall in FEF₂₅₋₇₅ of 14% is significant in the diagnosis of EIA in winter athletes. This lower limit was calculated by taking the mean post exercise change from baseline spirometry and subtracting 2 standard deviations. Lowering the FEF₅₀ cut off value in our data to ≥14% resulted in an increase in the sensitivity but a decrease in the specificity from 98% to 77%. Using a 14% cut off value, 13 athletes would have been diagnosed with EIA who did not meet the IOC-MC criterion of a 10% fall in FEV₁ from baseline values.

A further problem associated with the use of FEF₅₀ as a criterion measurement is that its reliability is dependent upon the constancy of FVC. Our results show that the mean fall in FEF₅₀ following bronchoconstriction was accompanied by a mean fall in FVC in athletes with EIA. The fall in FEF₅₀ seen in some of athletes following a bronchoprovocation test may therefore be partially attributable to a reduction in FVC. The reduction in FVC in asthmatic athletes may be due to the prolongation and discomfort associated with exhaling to residual volume during bronchoconstriction. Despite standard controls, this may cause the athlete to stop exhaling before reaching residual volume. This shortcoming further undermines the potential value of FEF₅₀ for diagnosing EIA.

In conclusion, the addition of FEF₅₀ to FEV₁ reduces the sensitivity of a diagnosis of EIA in elite athletes. Our data suggest that a more global measure of maximal expiratory airflow (FEV₁) provides the most sensitive and specific diagnosis of EIA, especially when the severity of the disease is thought to be mild. This would suggest that EIA is a disease that is associated with expiratory flow limitation in the larger and smaller airways of elite athletes. However, methodological issues associated with assessment of FEF₅₀ (reliance upon FVC) mean that this interpretation should be viewed cautiously. The authors suggest that future studies should investigate the efficacy of the IOC-MC criterion of a 10% fall in FEV₁ to define a more statistically justified cut off point for the diagnosis of EIA in elite athletes.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Cut off 26%</th>
<th>Cut off 14%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>98</td>
<td>77</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Predictive value of</td>
<td>98</td>
<td>80</td>
</tr>
<tr>
<td>positive test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficiency</td>
<td>81</td>
<td>81</td>
</tr>
</tbody>
</table>

≥26% fall in FEF₅₀ in the absence of a ≥10% in FEV₁ (ΔFEV₁ = 8.9%). Of the 83 athletes with a previous diagnosis of EIA, 33 failed to develop EIA (ΔFEV₁ < 10%) following bronchoprovocation challenge. Of the 33 athletes who had been referred for testing but had no previous diagnosis of EIA, 10 athletes presented with EIA following bronchoprovocation.

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The authors are grateful to the European Olympic Committee, UK Sport, British Olympic Medical Trust, Olympic Medical Institute, and Micro Medical Ltd.

Competing interests: none declared

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