ASTHMA

Mid-expiratory flow versus FEV_1 measurements in the diagnosis of exercise induced asthma in elite athletes

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Backround: A fall in FEV_1 of $\geqslant$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_{50}) might be used to supplement FEV_1 to improve the sensitivity and specificity of the diagnosis. A study was undertaken to investigate the response of FEF_{50} following EVH or exercise challenges in elite athletes as an adjunct to FEV_1.

Methods: Sixty six 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_1 of $\geqslant$10% and a fall in FEF_{50} of $\geqslant$26% were used as the cut off criteria for identification of EIA.

Results: There was a strong correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation ($r=0.94$, $p=0.000$). Sixty athletes had a fall in FEV_1 of $\geqslant$10% leading to the diagnosis of EIA. Using the FEF_{50} criterion alone led to 21 (35%) of these asthmatic athletes receiving a false negative diagnosis. The lowest fall in FEF_{50} in an athlete with a $\geqslant$10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criteria to $\geqslant$14% led to 13 athletes receiving a false positive diagnosis. Only one athlete had a fall in FEF_{50} of $\geqslant$26% in the absence of a fall in FEV_1 of $\geqslant$10% ($\Delta FEV_1 = 8.9\%$).

Conclusion: The inclusion of FEF_{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_{50} alone is insufficiently sensitive to diagnose EIA reliably in elite athletes.

Exercise induced asthma (EIA) occurs in approximately 90% of chronic asthmatics[1] and has previously been reported to occur in 7–50% of athletic individuals.[2–6] Asthmatic elite athletes currently require evidence of asthma to obtain a therapeutic use exemption certificate which enables them to use therapeutic doses of inhaled β_2 agonists in and out of competition.[7] EIA has previously been diagnosed by a number of challenge methods including exercise,[8 9] eucapnic voluntary hyperventilation (EVH),[10 11] methacholine,[12 13] histamine,[14] saline,[15] and mannitol.[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.[16 18 19] Exercise and EVH challenges are regarded as the most specific methods of diagnosing EIA in elite athletes.[11]

In all EIA tests recognised by the IOC-MC, forced expiratory volume in 1 second (FEV_1) is the parameter by which changes in maximal expiratory function are assessed, but no "gold standard" methodology exists for athletes or non-athletes.[20] Previous studies that have used FEV_1 to diagnose EIA have suggested using falls in FEV_1 ranging from 7% to 20% as cut off criteria.[21–23] The work carried out by Helenius *et al*[23] suggests that a fall of 10% in FEV_1 following an exercise test is not sensitive enough to diagnose EIA in elite athletes. Despite the absence of a "gold standard" methodology for diagnosing EIA in athletes, the IOC-MC has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls $\geqslant$10% from the baseline measurement.

It is possible that the addition of other measurements of expiratory lung function may provide greater sensitivity in the diagnosis of EIA. For example, forced expiratory flow between 25–75% of vital capacity (FEF_{25-75}) has been used in conjunction with FEV_1 to aid the diagnosis of EIA in children[24 25] and athletes.[8 26] Implicitly, FEV_1 measures expiratory flow at high and mid lung volumes, whereas FEF_{25-75} and forced expiratory flow at 50% of vital capacity (FEF_{50}) are markers of expiratory flow through middle lung volumes. It has been suggested that FEF_{25-75} and FEF_{50} are more sensitive to airway obstruction in the small airways than FEV_1.[27 28] Custovic *et al*[24] noted that cut off points for EIA in children (defined as the normal group mean value −2 SD) occurred with a fall in FEV_1 of >10% and a fall in FEF_{25-75} of >26%. In this study, the combined application of FEV_1 and FEF_{25-75} criteria enabled detection of all subjects with EIA. Furthermore, using both FEV_1 and FEF_{25-75} criteria, none of the subjects with allergic rhinitis or dermatitis presented with EIA. The fall in FEV_1 after exercise in children with allergic rhinitis was within the normal range ($\leqslant$2SD), but with a significantly lower mean value than control subjects. The study by Custovic *et al*[24] therefore provides promising evidence to support the addition of mid expiratory flow rates to FEV_1 in the diagnosis of EIA in children that might also be applied to elite athletes. FEF_{50} and FEF_{25-50} measurements are highly correlated and the ratio of the two is reasonably constant. Based on this finding, Bar-Yishay *et al*[29] suggested that reporting both measurements is unnecessary, and they suggested that FEF_{50} should be the preferred measure. This preference was based on the argument that FEF_{50} is easily and directly determined while FEF_{25-50} is a calculated

Abbreviations: EIA, exercise induced asthma; EVH, eucapnic voluntary hyperventilation; FEF_{50}, forced expiratory flow at 50% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

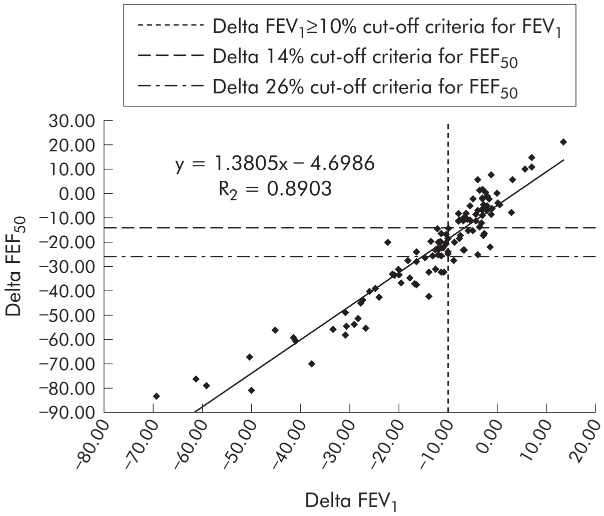

Figure 1 Delta FEV_1 versus delta FEF_{50}.

parameter that is affected by the spirometer manufacturer's choice of algorithm.

The purpose of the present study was to examine the role of FEF_{50} as an adjunct to FEV_1 in the diagnosis of EIA in elite athletes following a bronchoprovocation challenge.

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.[30] EVH challenges consisted of hyperventilating for 6 minutes at a rate of 85% maximal voluntary ventilation (30 × baseline FEV_1). The gas inspired during the EVH challenge was a medical gas containing 21% O_2, 5% CO_2 and 74% N_2.[31] 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 FEV_1 and FEF_{50} following either exercise or EVH were recorded and the change was calculated (Δ). A ΔFEV_1 of $\geq -10\%$ and ΔFEF_{50} of $\geq -26\%$ were considered cut off criteria for EIA diagnosis.[24]

Table 2 True and false positive and negative diagnoses based on FEF_{50} cut off value of 26%

True positive	39
True negative	55
Total true	94
False negative	21
False positive	1
Total false	22
Total with EIA	60
Total without EIA	56
Total	116

True positive = ΔFEV_1 of $\geq$10% and a fall in FEF_{50} of $\geq$26%.
True negative = ΔFEV_1 of $\geq$10% and did not have a fall in FEF_{50} of $\geq$26%.
False positive = ΔFEV_1 of $\leq$10% and a fall in FEF_{50} of $\geq$26%.
False negative = ΔFEV_1 of $\geq$10% and a fall in FEF_{50} of $\leq$26%.

Table 3 True and false positive and negative diagnoses based on FEF_{50} cut off value of 14%

True positive	51
True negative	43
Total true	94
False negative	9
False positive	13
Total false	22
Total with EIA	60
Total without EIA	56
Total	116

True positive = ΔFEV_1 of $\geq$10% and a fall in FEF_{50} of $\geq$14%.
True negative = ΔFEV_1 of $\geq$10% and did not have a fall in FEF_{50} of $\geq$14%.
False positive = ΔFEV_1 of $\leq$10% and a fall in FEF_{50} of $\geq$14%.
False negative = ΔFEV_1 of $\geq$10% and a fall in FEF_{50} of $\leq$14%.

RESULTS

There was a strong positive correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation ($r = 0.94$, $p = 0.000$). Sixty athletes (52%) had a ΔFEV_1 fall of $\geq$10% leading to the diagnosis of EIA (fig 1). Using the FEF_{50} criteria alone led to 21 (35%) asthmatic athletes receiving a false negative diagnosis; thus, 39 athletes met both FEV_1 and FEF_{50} criteria. The lowest fall in ΔFEF_{50} in an athlete with a $\geq$10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criterion to a $\geq$14% fall included 13 athletes whose ΔFEV_1 was not $\geq$10% (mean $\Delta FEV_1 = 5.7$, range −8.9 to −1.5). Only one athlete had a

Table 1 Mean (SD) changes in FEF_{50} and FVC following bronchoprovocation challenge

	FEF_{50} (l/s)		FVC (l)	
	Before	After	Before	After
Asthmatic	3.86 (0.92)	2.39 (0.84)**	4.99 (1.00)	4.45 (1.16)**
Non-asthmatic	4.79 (1.37)	4.43 (1.31)	4.81 (1.03)	4.65 (1.04)

Asthmatic athlete defined as having a $\geq$10% fall in FEV_1 following bronchoprovocation.
**Significantly different (p<0.05) from pre-test value.

Table 4 Effectiveness of FEF_{50} cut off criteria of 26% and 14%

	Cut off 26%	Cut off 14%
Specificity	98	77
Sensitivity	65	85
Predictive value of positive test	98	80
Efficiency	81	81

$\geqslant$26% fall in FEF_{50} in the absence of a $\geqslant$10% in FEV_1 ($\Delta FEV_1 = 8.9\%$).

Of the 83 athletes with a previous diagnosis of EIA, 33 failed to develop EIA ($\Delta FEV_1 < 10\%$) 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 FEF_{50} and forced vital capacity (FVC) before and after bronchoprovocation challenge are shown in table 1. FEF_{50} ($p = 0.000$) and FVC ($p = 0.000$) were significantly lower after bronchoprovocation in the asthmatic athletes. There was no significant change in FEF_{50} or FVC before and after bronchoprovocation challenge in athletes who did not have a fall in FEV_1 of $\geqslant$10%.

The specificity, sensitivity, predictive value of positive test and efficiency of FEF_{50} cut off criteria of 26% and 14% are shown in tables 2, 3 and 4, respectively.

DISCUSSION

This study shows that the addition of FEF_{50} 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 $\geqslant$10% fall in FEV_1, 21 (35%) would have received a false negative diagnosis using a combination of FEV_1 and FEF_{50} falls. Furthermore, only one athlete exceeded the criterion for FEF_{50} but not for FEV_1. Our study therefore suggests that FEF_{50} does not improve the diagnosis of EIA in elite athletes using the IOC-MC criteria.

In previous studies, measurements of FEF_{25-75} have been used to supplement FEV_1 in the diagnosis of EIA in children[24 25] and athletes.[8 26] The studies conducted on children have supported the addition of FEF_{25-75} measurements to improve the diagnosis of EIA. It has been suggested that FEF_{25-75} is a more sensitive measure of obstruction in the small airways than FEV_1.[32] Thus, EIA may be a disease that consistently affects the expiratory flow through the small airways. Fonseca-Guedes *et al*[25] noted that only 60% of children with "intermittent" EIA met the criteria for both FEV_1 and FEF_{25-75} compared with 94.4% of children with "severe persistent" EIA. They suggested that FEF_{25-75} is more likely to fall significantly than FEV_1 in children with mild EIA. Our data do not agree with this finding and suggest that FEV_1 is more likely to fall significantly in athletes with mild asthma. Indeed, only one athlete had a significant fall in FEF_{50} ($\geqslant$26%) in the absence of a significant fall in FEV_1, while 21 athletes had a significant fall in FEV_1 ($\geqslant$10%) in the absence of a significant fall in FEF_{50}. Only 39 athletes met both criteria for FEF_{50} and FEV_1, which would have resulted in 21 (35%) athletes (who met FEV_1 criteria) receiving a false negative diagnosis for EIA. The reduced sensitivity found following the inclusion of the FEF_{50} measurement suggests that, in elite athletes with mild EIA, expiratory airflow is just as likely to be restricted in the larger airways as in the smaller airways. It is therefore appropriate to assess expiratory flow using an index of function for both the larger and smaller airways of the lung—that is, FEV_1.

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*[8] suggested that a fall in FEF_{25-75} 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 FEF_{50} cut off value in our data to $\geqslant$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 FEV_1 from baseline values.

A further problem associated with the use of FEF_{50} as a criterion measurement is that its reliability is dependent upon the constancy of FVC. Our results show that the mean fall in FEF_{50} following bronchoconstriction was accompanied by a mean fall in FVC in athletes with EIA. The fall in FEF_{50} 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 FEF_{50} for diagnosing EIA.

In conclusion, the addition of FEF_{50} to FEV_1 reduces the sensitivity of a diagnosis of EIA in elite athletes. Our data suggest that a more global measure of maximal expiratory airflow (FEV_1) 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 FEF_{50} (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 FEV_1 to define a more statistically justified cut off point for the diagnosis of EIA in elite athletes.

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REFERENCES

1 **Lacroix V**. Exercise induced asthma. *Physician Sports Med* 1999;**27**:75–92.
2 **Weiler J**, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Olympic Games. *J Allergy Clin Immunol* 1998;**102**:722–6.
3 **Wilber R**, Rundell K, Szemdra L, *et al*. Incidence of exercise induced bronchospasm in Olympic winter sport athletes. *Med Sci Sports Exerc* 2000;**32**:732–7.
4 **Larsson K**, Ohlsen P, Larrson L, *et al*. High prevalence of asthma in cross-country skiers. *BMJ* 1993;**307**:1326–9.
5 **Helenius I**, Tikkanen H, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med* 1998;**32**:125–9.
6 **Dickinson J**, Whyte G, McConnell A, *et al*. Impact of changes in the IOC-MC asthma criteria: a British perspective. *Thorax* 2005;**60**:629–32.
7 **Medical Commission of the International Olympic Committee**. *IOC's medical code*. Lausanne: International Olympic Committee, 2002.

8 **Rundell K**, Wilber R, Szemedra L, *et al*. Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. *Med Sci Sports Exerc* 2000;**32**:309–16.
9 **Anderson S**, Schoeffel R, Follet R, *et al*. Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. *Eur J Respir Dis* 1982;**63**:459–71.
10 **Rundell K**, Anderson S, Spiering B, *et al*. Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. *Chest* 2004;**125**:909–15.
11 Anderson S, Fitch K, Perry C, et al. Responses to bronchial challenge submitted for approval to use inhaled beta2-agonists before an event at the 2002 Winter Olympics *J Allergy Clin Immunol* 2003;**111**:45–50.
12 **Wagner E**, Jacoby D. Methocholine causes reflex bronchoconstriction. *J Appl Physiol* 1999;**86**:294–7.
13 **Scanlon P**, Beck K. Methacholine inhalation challenge. *Mayo Clinic Proc* 1994;**69**:1118–9.
14 **Anderton R**, Cuff M, Frith P, *et al*. Bronchial responsiveness to inhaled histamine and exercise. *J Allergy Clin Immunol* 1979;**63**:315–20.
15 **Smith S**, Anderson S. A comparison between airway response to isocapnic hyperventilation and hypertonic saline in subjects with asthma. *Eur Respir J* 1990;**2**:36–43.
16 **Anderson S**, Brannan J, Spring J, *et al*. A new method for bronchial-provocation testing in asthmatic subjects using dry powder of mannitol. *Am J Respir Crit Care Med* 1997;**156**:758–65.
17 **Brannan J**, Lee K, Anderson S, *et al*. Responsiveness to mannitol in asthmatic subjects with exercise- and hyperventilation-induced asthma. *Am J Respir Crit Care Med* 1998;**158**:1120–6.
18 **Avital A**, Springer C, Bar-Yishay E, *et al*. Adenosine methacholine and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. *Thorax* 1995;**50**:511–6.
19 **Bhagat R**, Grunstein M. Comparison of responsiveness to methacholine, histamine and exercise subgroups of asthmatic children. *Am Rev Respir Dis* 1984;**129**:221–4.
20 **Godfrey S**. Clinical and physiological features. In: McFadden E, eds. *Exercise-induced asthma*. New York: Marcel Davis, 1999:11–45.
21 **Anderson S**, Connolly N, Godfrey S. Comparison of bronchoconstriction induced by cycling and running. *Thorax* 1971;**26**:396–401.
22 **Eggleston P**, Rosenthal R, Anderson S, *et al*. Guidelines for the methodology of exercise challenge testing of asthmatics. *J Allergy Clin Immunol* 1979;**64**:642–5.
23 **Helenius I**, Tikkanen H, Haahtela T. Exercise-Induced bronchospasm at low temperature in elite runners. *Thorax* 1996;**51**:628–9.
24 **Custovic A**, Arifhodzic N, Robinson A, *et al*. Exercise testing revisited. The response to exercise in normal and atopic children. *Chest* 1994;**105**:1127–32.
25 **Fonseca-Guedes C**, Cabral A, Martins M. Exercise-induced bronchospasm in children: Comparison of FEV_1 and FEF_{25-75} responses *Pediatr Pulmonol* 2003;**36**:49–54.
26 **Rundell K**, Im J, Wilber D, *et al*. Mid expiratory flow rates of cold weather athletes with exercise induced asthma. *Med Sci Sports Exerc* 2001;**33**:512.
27 **McFadden E**, Linden D. A reduction in maximal mid-expiratory flow rate: a spirographic manifestation of small airway disease. *Am J Med* 1972;**52**:725–37.
28 **Lebecaque P**, Kiakulanda P, Coates A. Spirometry in the asthmatic child; is FEF_{25-75} a more sensitive test than FEV_1/FVC? *Pediatr Pulmonol* 1993;**16**:19–22.
29 **Bar-Yishay E**, Amirav I, Goldberg S. Comparison of maximal mid-expiratory flow rate and forced expiratory flow at 50% of vital capacity in children. *Chest* 2003;**123**:731–5.
30 **American Thoracic Society**. Guidelines for methocholine and exercise challenge testing—1999. *Am J Respir Crit Care Med* 2000;**161**:309–29.
31 **Anderson S**, Argyros G, Magnussen H, *et al*. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *Br J Sports Med* 2001;**35**:344–7.
32 **McFadden E**, Linden D. A reduction in maximal mid-expiratory flow-rate: a spirographic manifestation of small airways disease. *Am J Med* 1972;**52**:725–37.

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