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MID-EXPIRATORY FLOW VS FEV_1 MEASUREMENTS IN THE DIAGNOSIS OF EXERCISE INDUCED ASTHMA IN ELITE ATHLETES

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Abstract

Backround: A fall in FEV_1 of $\geq$10% following bronchoprovocation (Eucapnic Voluntary Hyperventilation (EVH) or exercise) is regarded as the gold standard criterion for diagnoses of 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 sensitivity and specificity of EIA diagnosis.

Purpose: To investigate the response of FEF_{50} following EVH or exercise challenges, in elite athletes, as an adjunct to FEV_1.

Methods: Following local ethics committee approval and written informed consent, 66 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 ≥10% and a fall in FEF_{50} ≥26% was employed 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 demonstrated a fall in FEV_1 ≥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 ≥10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criteria to ≥14% led to 13 athletes receiving a false positive diagnosis. Only one athlete had a ≥26% fall in FEF_{50} in the absence of a ≥10% in FEV_1 (ΔFEV_1 = 8.9%).

Conclusion: Our study shows that including FEF_{50} in the diagnosis of EIA in elite athletes reduces sensitivity. The addition of FEF_{50} does not enhance the sensitivity or specificity in the diagnosis of EIA in elite athletes. Further, use of FEF_{50} alone is insufficiently sensitive to reliably diagnose EIA in elite athletes.

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Exercise-induced asthma (EIA) occurs in approximately 90% of chronic asthmatics [1] and has previously been reported to occur in 7-50% of athletic populations.[2][3][4][5][6] Asthmatic elite athletes, currently require evidence of asthma to obtain a Therapeutic Use Exemption Certificate, which enables the athlete to use therapeutic doses of inhaled β_2-Agonists in and out of competition.[7] EIA has previously been diagnosed through a variety 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 EIA diagnosis in elite athletes.[11]

In all EIA tests recognised by the IOC-MC, forced expiratory volume in one 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 cut off criteria ranging from 7-20% falls in FEV_1.[21][22][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 diagnosis of EIA in athletes, the IOC-MC has ruled that an exercise or EVH challenge is positive for EIA when the FEV_1 falls ≥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 >10% fall in FEV_1 and >26% fall in FEF_{25-75}. 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 (≤2SD), but with a significantly lower mean value than control subjects. Thus, Custovic et al.[24] study provides promising evidence supporting 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. The measurements FEF_{50} and FEF_{25-50} are highly correlated and the ratio of the two is reasonably constant. Based on this finding, Bar-Yishay et al.[29] suggested that reporting

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both measurements is unnecessary, and they suggested that FEF_{50} be the preferred measure. This preference was based upon the argument that FEF_{50} is easily and directly determined, whilst FEF_{25-50} is a calculated parameter that is affected by the spirometer manufactures' 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.

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Methods

Following ethical approval from Harrow local research ethics committee, 66 male (Mean ±SD, age 25.1±4.9 yrs, height 180.7±7.8 cm, body mass 77.3±12.5 Kg) and 50 female (age 24.3+5.4 yrs, height 168.2+7.9 cm, body mass 62.6+9.9 Kg) elite summer and winter athletes, 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 two weeks following a respiratory infection and at least 12 hours following a training session.

Each athlete completed either an exercise or eucapnic voluntary hyperventilation (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 x 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 challenge 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 ≥-10% and ΔFEF_{50} of ≥-26% were considered cut off criteria for EIA diagnosis.[24]

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Results

There was a strong positive correlation between ΔFEV_1 and ΔFEF_{50} following bronchoprovocation (r=0.94, p=0.000). Sixty athletes (52%) demonstrated a ΔFEV_1 fall of ≥10% leading to the diagnosis of EIA (see figure 1). Using the FEF_{50} criteria alone led to 21 (35%) asthmatic athletes receiving 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 ≥10% fall in FEV_1 was 14.3%. Reducing the FEF_{50} criterion to a ≥14% fall included 13 athletes whose ΔFEV_1 was not ≥10% (mean ΔFEV_1= 5.7, range -8.9 to -1.5). Only one athlete had a ≥26% fall in FEF_{50} in the absence of a ≥10% in FEV_1 (ΔFEV_1 = 8.9%).

Of the 83 athletes with a previous diagnosis of EIA, 33 failed to present EIA (ΔFEV_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 FVC pre and post bronchoprovocation challenge are reported in table 1. FEF_{50} (p=0.000) and FVC (p=0.000) are significantly lower post bronchoprovocation in the asthmatic athletes. There was no significant change in FEF_{50} or FVC pre and post bronchoprovocation challenge in athletes who did not have fall in FEV_1 ≥10%.

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

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Table 1: Changes in FEF_{50} and FVC following bronchoprovocation challenge

	FEF_{50} (l/sec)		FVC (l)	
	Pre (mean±SD)	Post (mean±SD)	Pre (mean±SD)	Post (mean±SD)
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 ≥10% fall in FEV_1 following bronchoprovication.
**= significantly different ($p<0.05$) from pre test value

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Table 2: True and false positive and true and false negative diagnoses based on FEF_{50} cut-off 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 = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≥26%
True Negative = ΔFEV1 of ≥10% and did not have a fall in FEF_{50} of ≥26%
False Positive = ΔFEV1 of ≤10% and a fall in FEF_{50} of ≥26%
False Negative = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≤26%

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Table 3: True and false positive results based on FEF_{50} cut-off 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 = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≥14%
True Negative = ΔFEV1 of ≥10% and did not have a fall in FEF_{50} of ≥14%
False Positive = ΔFEV1 of ≤10% and a fall in FEF_{50} of ≥14%
False Negative = ΔFEV1 of ≥10% and a fall in FEF_{50} of ≤14%

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Table 4: The Effectiveness of FEF_{50} cut-off criteria of 26% and 14%.

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

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Discussion

Our study demonstrates 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 ≥10% fall in FEV_1, 21 (35%) athletes would have received false negative diagnosis if a combination of FEV_1 and FEF_{50} falls were required for diagnosis. Further, only one athlete exceeded the criterion for FEF_{50}, but not for FEV_1. Our study therefore suggests FEF_{50} does not improve the diagnosis of EIA in elite athletes via the IOC-MC criteria.

In previous studies, measurements of FEF_{25-75} have been employed 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 FEF_{25-75} is a more sensitive measure of obstruction in the small airways than FEV_1.[32] Thus, EIA maybe 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 compared to 94.4% of children with 'severe persistent' EIA met the criteria for both FEV_1 and FEF_{25-75}. Fonseca-Guedes et al.[25] suggest FEF_{25-75} was more likely to fall significantly than FEV_1 in children with mild EIA. In contrast, our data are inconsistent with this finding and suggest that FEV_1 is more likely to fall significantly in athletes with mild asthma. Indeed, only 1 athlete had a significant fall in FEF_{50} (≥26%) in the absence of a significant fall in FEV_1, compared to 21 athletes who had a significant fall in FEV_1 (≥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%) of athletes (who met FEV_1 criteria) receiving a false negative diagnosis for EIA. The reduced sensitivity demonstrated following the inclusion of 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 it is in the smaller airways. Thus, it is most appropriate to assess expiratory flow using an index of function for both the larger and smaller airways of the lung, i.e. FEV_1.

There have been a number of studies conducted examining the diagnosis of EIA in athletes; however, these have not specifically used mid-expiratory flow rates as a criterion measurement to diagnose EIA. 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 criterion in our data to ≥14% resulted in an increase in the sensitivity, however this came at a cost of a lower specificity of the measurement, from 98% to 77%. Using a 14% criterion, 13 athletes would have been diagnosed 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 constancy of FVC . Our results demonstrate that the mean fall in FEF_{50} following bronchoconstriction

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was accompanied by a mean fall in FVC in EIA athletes. Therefore, the fall in FEF_{50} that is evident in some of the athletes following a bronchoprovocation test may be partially attributable to a reduction in FVC. The reduction of 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 prior to reaching residual volume. This shortcoming further undermines the potential value of FEF_{50} for diagnosis of EIA.

Conclusion: The addition of FEF_{50} to FEV_1 reduces the sensitivity of EIA diagnosis 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 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 EIA diagnosis in elite athletes.

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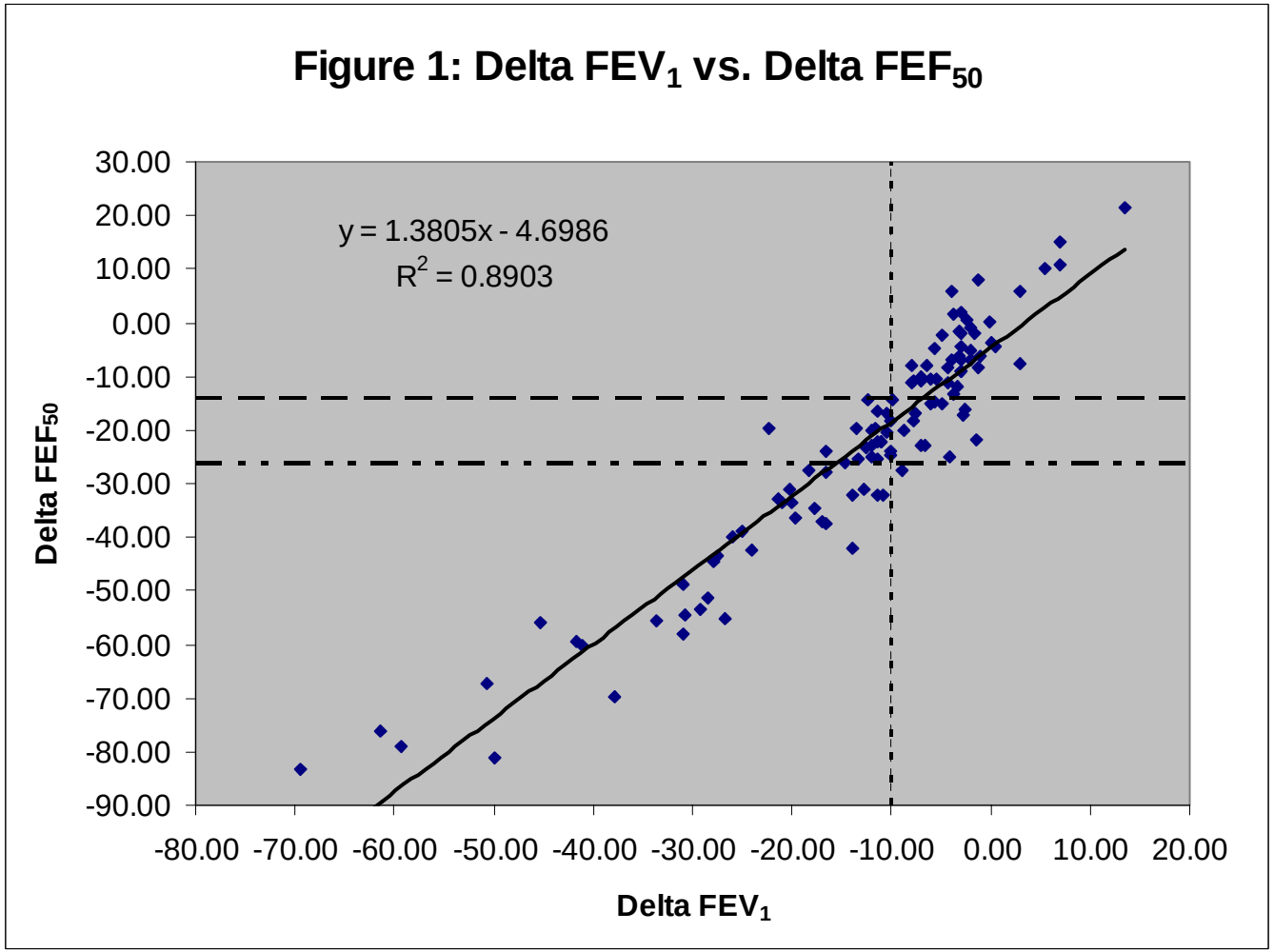
Figure 1: Delta FEV_1 vs. Delta FEF_{50}



Delta FEV1≥10% Cut-off criteria for FEV_1

Delta 14% cut-off criteria for FEF_{50}

Delta 26% cut-off criteria for FEF_{50}

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