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Use of Isovolume Flow Curves in the Detection of Exercise-Induced Bronchospasm

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Abstract. A simple 9-min progressive cycle ergometer test revealed exercise-induced bronchospasm in 23 of 29 asthmatic subjects (80%) in terms of a 15% decrement in the isovolume forced expiratory flow rate at 50% of the baseline vital capacity ($\dot{V}_{max\ iso\ 50\%VC}$). A similar percentage was detected by the $\dot{V}_{max\ iso\ 60\%TLC}$ (78%), but that found with the FVC (35%) and $FEV_{1.0}$ (48%) was somewhat lower. The maximum change of $\dot{V}_{max\ iso\ 50\%VC}$ following exercise in normal subjects was –5.2 ± 2.1%. The $\dot{V}_{max\ iso\ 50\%VC}$ thus combines sensitivity with specificity, and seems a very suitable procedure for routine clinical use. Asthmatics showing a positive reaction to this test were distinguished by poor pre-exercise lung function.

Introduction

Exercise-induced bronchospasm (EIB) is a common finding in asthmatics [1]. Indeed, some authors maintain that all asthmatic patients will show a significant increase of airway resistance, given a suitable combination of vigorous sustained exercise and a sensitive test procedure [2, 3]; the assessment of EIB may thus help to establish a diagnosis of asthma in doubtful cases. In 50–70% of cases the affected individuals remain unaware that airflow resistance has increased [4, 5], so that careful testing of pulmonary function plays an important role in the detection of this condition.

The most powerful stimulus triggering EIB is free running in cold, dry air [6]. However, problems of monitoring the subject restrict the application of this technique, particularly in older adults where an exercise electrocardiogram is desirable. Treadmill running also seems more likely to induce bronchospasm than a comparable intensity of cycle ergometer work [7]; nevertheless, the cycle ergometer offers certain advantages over the treadmill with respect to clinical testing, including (i) lower cost, (ii) easier monitoring of the patient, (iii) more rapid familiarization with the procedure, (iv) less danger of injuries, and (v) more accurate quantitation of work output

Table I. General characteristics of the asthmatic group (n = 29)

Characteristics		Treatment		Pulmonary function (mean ± SD)	
Mean age, years	35.0 ± 7.6	prednisone (oral)	7/29 (24%)	FVC[1]	95 ± 19
Sex ratio (M/F)	13/16	beclomethasone (inhaled)	11/29 (38%)	$FEV_{1.0}$[1]	72 ± 23
Duration of asthma, years	17 ± 13	oral and/or inhaled steroids	11/29 (38%)	$FEV_{1.0}$/FVC, %	64 ± 14
Cigarette smokers (at the time of study)	9/29 (31%)	disodium cromoglycate	5/29 (17%)	FRC[1]	104 ± 25
				RV[1]	122 ± 40
Chronic bronchitis (according to MRC criteria)	8/29 (28%)			TLC[1]	104 ± 15
				RV/TLC, %	35 ± 10
				$\dot{V}_{max\ 50\%VC}$[1]	50 ± 29
				$\dot{V}_{max\ 25\%VC}$[1]	35 ± 23
				$\dot{V}_{max\ 60\%TLC}$, l/s	1.57 ± 1.08
				change in $FEV_{1.0}$ with bronchodilator, %	29 ± 24

FRC = Functional residual capacity; RV = residual volume.

1 Percent of predicted value, based on norms for Toronto laboratories adopted by Inter-Hospital Respiratory Disease Committee.

[8, 9]. Localized muscle fatigue rather than cardiovascular or respiratory function may limit the maximal amount of work performed on a cycle ergometer [10], but a sustained and vigorous submaximal exercise test is usually sufficient for the assessment of EIB.

Traditionally, a decrease in either 1-second forced expiratory volume ($FEV_{1.0}$) [4, 11–13] or peak flow rate [14] has been used to detect EIB. The present paper examines the use of a simple yet more sensitive method of detecting EIB (the expiratory flow rate at 50% of the pre-exercise vital capacity, $\dot{V}_{max\ iso\ 50\%\ VC}$). It is suggested that the use of this test following submaximal cycle ergometer exercise allows the detection of EIB in a high proportion of asthmatics while using relatively simple, noninvasive procedures.

Materials and Methods

Subjects

The subjects studied were 13 male and 16 female adult asthmatics of varying degrees of severity (table I). Asthma was diagnosed according to the standard criteria used at the Gage Research Institute, namely (a) a history consistent with intermittent diffuse airway obstruction with (b) diffuse expiratory rhonchi and/or reversible airway obstruction indicated by a >15% increase of $FEV_{1.0}$ or $\dot{V}_{max\ 50\ VC}$ 20 min following four inhalations of salbutamol [2-t-butylamino-1-(4-hydroxy-3-hydroxy-methyl) phenyl ethanol]. Concomitant chronic bronchitis was not a contraindication to participation in the study.

Table II. Characteristics of the 6 normal control subjects (mean ± SD of data)

Age, years	27.2 ± 2.1	FRC[1]	83.3 ± 19.3
FVC[1]	103.3 ± 20.2	RV[1]	80.3 ± 23.0
$FEV_{1.0}$[1]	93.5 ± 13.5	TLC[1]	97.2 ± 19.9
$\dot{V}_{max\ iso\ 50\%VC}$[1]	92.3 ± 38.2	RV/TLC, %	22.6 ± 3.9
$\dot{V}_{max\ iso\ 25\%VC}$[1]	68.7 ± 25.1		

[1] Percent of predicted value, based on norms for Toronto Laboratories adopted by Inter-Hospital Respiratory Disease Committee.

Clinical information was obtained from patient files consisting of a standard documentation format. Subjects were tested regardless of the degree of airway obstruction, but with the proviso that their asthma was in a stable condition. Bronchodilator medication and disodium cromoglycate were withheld for 4 h before testing, but the normal schedule of oral and/or inhaled corticosteroids was continued as usual.

Data were also obtained on a small control sample of 3 male and 3 female nonsmokers; these were aged 25–31 years, with (a) no history of asthma, (b) a normal chest on physical examination, and (c) normal pre-exercise pulmonary function data (table II).

Pulmonary Function Tests

Initial lung volumes were determined by the standard helium dilution technique, using a Collins modular analyzer; all tests were continued until helium concentrations had equilibrated. Maximum expiratory flow-volume curves were recorded with a wedge spirometer equipped with an auxiliary timing device to mark $FEV_{1.0}$; display was by storage oscilloscope, the latter measurements being taken at rest and $2^1/_2$, 5, 10, 15 and 20 min after exercise.

Given the reciprocal relationship between airway resistance and lung volume, flow rates should be reported at a constant lung volume. Since forced vital capacity (FVC) changes after bronchoconstriction [15], there are difficulties in interpretation of the conventional $\dot{V}_{max\ 50\%\ VC}$ measurement in the post-exercise period. An alternative is to determine flow rates at 60% of total lung capacity ($\dot{V}_{max\ 60\%TLC}$). For this purpose, the TLC should be measured simultaneously with flow rates; however, to do this repetitively for 20 min after exercise would be cumbersome and impractical for clinical use. Changes of TLC after exercise are usually small in normal subjects and mild asthmatics [16], although larger effects have sometimes been reported in more severe disease [17]. We have thus matched all flow-volume curves at TLC, measuring flow rates at 50% of the initial VC (the $\dot{V}_{max\ iso\ 50\%\ VC}$) and 60% of the initial TLC (the $\dot{V}_{max\ iso\ 60\%\ TLC}$).

In accordance with previous tradition [1], we arbitrarily classed as a 'reactor' any subject who showed a 15% or more decline of a given test of lung function at any time after exercise. Note was taken of the maximum percentage change, and the time at which this developed.

Exercise Test

All subjects carried out a progressive submaximal exercise test on a Von Döbeln/Monark mechanically-braked cycle ergometer. Three work loads, each of 3 min duration, were adjusted to 45, 60 and 75% of maximum oxygen intake as judged from the heart rate response to the required exercise. For simplicity, all tests were carried out at normal laboratory temperature (22 ± 2 °C) with no specific control of humidity.

Other Procedures

A physical examination was completed, along with a 12-lead resting electrocardiogram, prior to the exercise testing. Paired t tests and linear regressions were employed in the statistical analysis of the results.

Table III. Comparison of initial pulmonary function status between EIB 'reactors' and 'non-reactors' as defined by $\dot{V}_{MAX\ iso\ 50\%VC}$ Test; data for 29 asthmatic subjects (mean ± SD)

Variable	Reactors	Nonreactors	p
FVC, % predicted	90.0 ± 14.9	101.3 ± 21.8	0.1–0.05
$FEV_{1.0}$, % predicted	62.2 ± 17.9	83.7 ± 25.1	<0.02
$FEV_{1.0}$/FVC	58.7 ± 12.4	69.5 ± 13.5	<0.005
$\dot{V}_{iso\ 50\%VC}$, % predicted	36.0 ± 21.7	66.8 ± 29.1	<0.005
$\dot{V}_{iso\ 25\%VC}$, % predicted	23.8 ± 12.6	49.5 ± 24.2	<0.005

Results

Sensitivity of Various Tests to EIB

On the basis of a 15% reduction in the $\dot{V}_{max\ iso\ 50\%\ VC}$ following our standard exercise test, 80% of the asthmatic patients (23 of 29) would have been classed as 'reactors'. The mean age of the two groups was similar (34.7 and 34.2 years, respectively), while the two groups contained similar proportions of smokers ($\chi^2 = 0.68$) and of men and women ($\chi^2 = 1.36$). The history of asthma had a duration of 20.6 years in the reactors, compared with 12.9 years in the other group ($0.1 > p > 0.05$). Furthermore, the reactors had significantly lower values for their pre-exercise $\dot{V}_{max\ 50\%\ VC}$, $\dot{V}_{max\ 25\%\ VC}$, and $FEV_{1.0}$ relative to the other group (table III).

The percentages of reactors detected by the other pulmonary function tests were FVC 35%, $FEV_{1.0}$ 48%, and $\dot{V}_{max\ iso\ 60\%\ TLC}$ 78%; however, the $\dot{V}_{max\ iso\ 60\%\ TLC}$ could not be measured in 2 patients, since their residual volume was greater than 60%TLC.

The $\dot{V}_{max\ iso\ 50\%\ VC}$ test showed not only sensitivity, but also specificity in detecting EIB. None of the control subjects showed a 15% decrease of $\dot{V}_{max\ iso\ 50\%\ VC}$ at any time after exercise. The maximum percent change seen in controls averaged –5.2 ± 2.1%, and the largest change for a control subject was –8% (fig. 2).

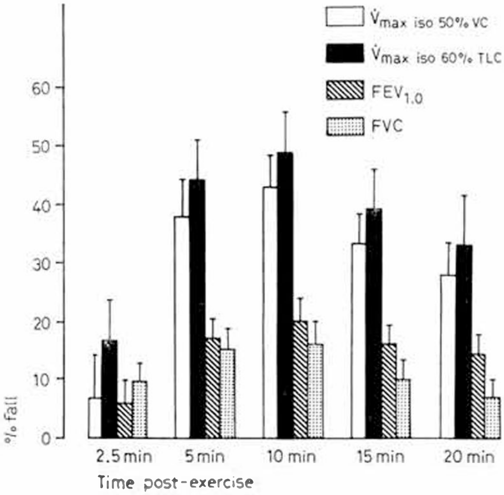

Fig. 1. Time course of changes in pulmonary function. Mean ± SE of data for 23 asthmatic 'reactors' following standard exercise test.

Time Course of Changes in Pulmonary Function

Examining data for the 23 'reactors' on the $\dot{V}_{max\ iso\ 50\%\ VC}$ test, we found the largest changes of pulmonary function 5 and 10 min post-exercise (fig. 1). $\dot{V}_{max\ iso\ 60\%\ TLC}$

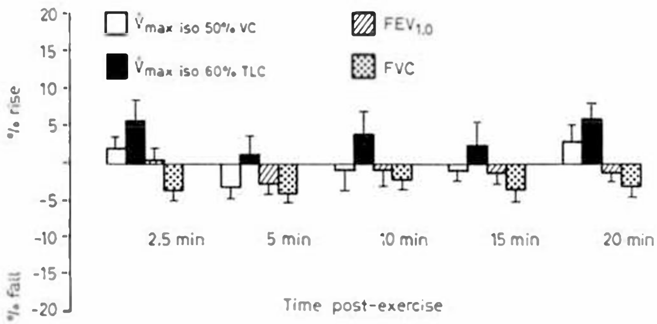

Fig. 2. Time course of changes in pulmonary function in normal subjects after standard exercise test. Mean $\pm$ SE of data.

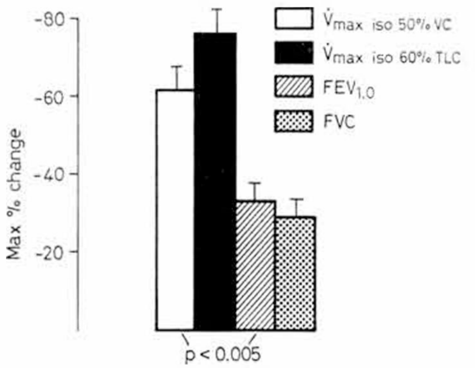

Fig. 3. Maximum exercise-induced changes of airflow variables in patients showing fall of $FEV_{1.0}$ greater than 15% (n = 14).

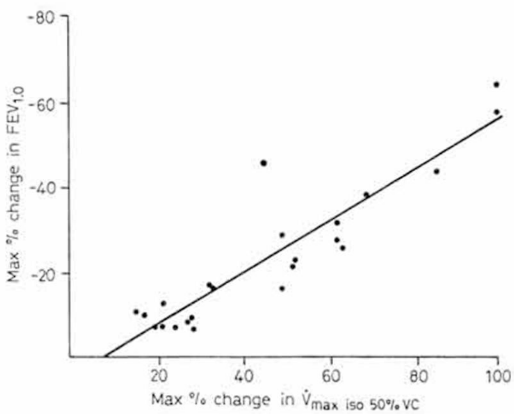

Fig. 4. Correlation between larger exercise-induced fall $\dot{V}_{max\ iso\ 50\%VC}$ and $FEV_{1.0}$. Linear regression, fitted by method of least squares, to data for 23 'reactors'. Slope: 0.602; y intercept: 4.83; r: 0.917.

and $\dot{V}_{max\ iso\ 50\%\ VC}$ showed the largest average decreases, changes in these two measurements running closely parallel with each other (coefficient of correlation for the maximum percent change in these two values, $r \pm S_r = 0.89 \pm 0.10$, $p < 0.001$).

Decreases of $FEV_{1.0}$ and FVC were smaller; 10 min post-exercise, the average change of $FEV_{1.0}$ was –13.7%, and at 20 min it averaged –9.0%. The maximum change of $FEV_{1.0}$ (irrespective of time post-exercise) averaged –27.6% for 'reactors' to the $\dot{V}_{max}$ test, and –3.0% for 'nonreactors'. Despite the difference in magnitude of the decrease in $\dot{V}_{max\ iso\ 50\%\ VC}$ and $FEV_{1.0}$ ($p < 0.005$, even if analysis was restricted to 14 subjects showing a drop in $FEV_{1.0}$ > 15%; fig. 3), the decrease of $\dot{V}_{max\ iso\ 50\%\ VC}$ was closely correlated with the maximum percent change of $FEV_{1.0}$ (fig. 4; r = 0.92 ± 0.9, $p < 0.001$).

Relationship of EIB to Initial Pulmonary Function Status

Taking data for all 29 asthmatic subjects, the maximum percent change in $\dot{V}_{max\ iso\ 50\%\ VC}$ was significantly larger among those with a baseline $\dot{V}_{max\ 50\%\ VC}$ less than 50% of predicted (–22.2%) than in those with a baseline $\dot{V}_{max\ 50\%}$ exceeding 50% of predicted (–10.2%; table IV). In

Table IV. Relationship between baseline $\dot{V}_{MAX\ 50\%VC}$ and degree of EIB data for 29 asthmatic subjects

	Baseline $\dot{V}_{max\ iso\ 50\%VC}$		p
	<50% predicted (n = 14)	>50% predicted (n = 15)	
Maximum percent change in $\dot{V}_{max\ iso\ 50\%VC}$	$-45 \pm 38\%$	$-22 \pm 32\%$	<0.05
Age, years	38 ± 7	32 ± 7	<0.025
Duration of asthma, years	25 ± 14	10 ± 9	<0.005

contrast, when classified by initial $FEV_{1.0}$, the difference was not significant. The group with a baseline $\dot{V}_{max\ 50\%\ VC}$ less than 50% of predicted was older, and had a significantly longer history of asthma than the other group. However, when considered alone, neither age nor duration of asthma history were correlated with the degree of EIB.

Despite the apparent influence of initial pulmonary function status upon EIB, the linear correlation between baseline $\dot{V}_{max\ 50\%}$ and maximum percent change in this variable was poor ($r = 0.21$ for entire sample; $r = -0.34$ if restricted to reactors). Only 20 of the 29 patients gave a clinical history of EIB; the correlation between such a history and the change in $\dot{V}_{max\ iso\ 50\%\ VC}$ was not statistically significant.

Discussion

The present results confirm that EIB is a very common occurrence in asthma, and emphasize that a clinical history alone is not a reliable method of detecting EIB, except in severe cases. Epidemiologists have stressed that ancillary procedures must be assessed in terms of their sensitivity and [18]. The criterion that we have adopted – a 15% exercise-induced decrease of specificity, with a view to minimizing both false positive and false negative diagnoses [18]. The criterion that we have adopted – a 15% exercise-induced decrease of $\dot{V}_{max\ iso\ 50\%\ VC}$ – is arbitrary, and does not necessarily distinguish distinct populations of 'reactors' and 'nonreactors'. Our data suggest it is a fairly good dividing point, since 80% of asthmatics showed a decrease of flow greater than 15% during exercise, whereas no subject in the control group had a change larger than 8%; however, it remains desirable to verify this limit of normality on a larger control sample. The sensitivity would be increased only slightly by lowering the criterion to a 10% decrease of $\dot{V}_{max\ iso\ 50\%\ VC}$ (83% of asthmatics reacting), and there would be a loss of specificity, since from the standard deviation of our normal data, we might then expect one diagnosis of EIB in about 88 normal subjects.

The yield of positive tests in our asthmatics compares favorably with the 75% reported for a single treadmill test; while the proportion of reactors can be increased to 95% by repeated treadmill testing [2, 3], it has yet to be shown that such exhaustive investigation does not also increase the yield of false positive information. Certainly, our data indicate that a simple cycle ergometer test, if coupled to the measurement of $\dot{V}_{max\ iso\ 50\%\ VC}$, provides a very practical clinical procedure for diagnosis of EIB, even in subjects where the degree of spasm is so slight that no symptoms are reported, and the condition cannot be detected by simple spirometry.

Our findings indicate that both the $\dot{V}_{max\ iso\ 50\%\ VC}$ and the $\dot{V}_{max\ iso\ 60\%\ TLC}$ provide a more sensitive indicator of EIB than does the determination of $FEV_{1.0}$. However, the first measurement is to be preferred, since not all patients can carry out a $\dot{V}_{max\ iso\ 60\%\ TLC}$. Although the standard error of the response is somewhat greater for the flow-volume loop than for the forced expiratory volume measurement, the significance of the decrease in flow is substantially greater for $\dot{V}_{max\ iso\ 50\%\ VC}$ than for $FEV_{1.0}$. It might be objected that our analysis was biased in this sense by use of the $\dot{V}_{max}$ test to define 'reactors'. However, the conclusion is sustained if the criterion of a 'reactor' is taken as a 15% decrease of $FEV_{1.0}$. The superiority of the flow-volume curve as a means of detecting bronchospasm is in accord with the observations of *Bouhuys* et al. [19] on flax dust challenges, although these authors used the $\dot{V}_{max\ 50\%\ VC}$ rather than the $\dot{V}_{max\ iso\ 50\%\ VC}$.

Previous authors have disagreed as to the influence of initial function upon the degree of EIB. *Haynes* et al. [20] reported a correlation between airway obstruction and the magnitude of EIB, but *Godfrey* [21] found no such relationship. Part of the disagreement may relate to the method of calculating results. Our study suggest that those with a baseline $\dot{V}_{max\ 50\%\ VC}$ less than 50% of the predicted value have an increased percentage change of flow, but that the absolute change (l/s) is similar to that observed with a $\dot{V}_{max\ 50\%\ VC}$ higher than 50% of the predicted value. Possible factors predisposing to a greater relative response in those with narrow airways include (i) an increase in the proportion of turbulent airflow, (ii) a laminar airflow resistance proportional to the fourth power of airway radius, and (iii) a greater susceptibility of the airways to the cold, dry air that may be inhaled during exercise.

In conclusion, the $\dot{V}_{max\ iso\ 50\%\ VC}$ combines the epidemiological desiderata of sensitivity and specificity, offering a very practicable test for the routine diagnosis of EIB in both mild and more severe cases of airway obstruction.

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