

# Reproducibility of flow rates measured with low density gas mixtures in exercise-induced bronchospasm

STEPHEN G SPIRO, C WARREN BIERMAN, IAN S PETHERAM

*From the Department of Respiratory Medicine, Rayne Institute, University College Hospital, London*

**ABSTRACT** We have studied the reproducibility of the change in maximum expiratory flow rates after breathing helium/oxygen (He/O<sub>2</sub>) mixtures in 12 asthmatics at rest and after exercise. Each subject performed four identical exercise tests which caused a similar degree of exercise-induced bronchospasm (EIB) on each occasion. We compared flow rates at 50% of the vital capacity (V50) breathing He/O<sub>2</sub> to those breathing air at rest, and with the lowest V50 on air after exercise. Those subjects showing an increase of greater than 20% in V50 with He/O<sub>2</sub> compared to the corresponding air value were termed "responders". At rest the responder status after He/O<sub>2</sub> was more consistent than during EIB. Six subjects were non-responders consistently on up to 12 separate measurements at rest while the other five subjects were non-responders on all but one occasion and the remaining subject a responder on seven of eight measurements. During EIB all but one subject showed a He/O<sub>2</sub> response. A response was seen consistently in six subjects but the actual percentage change in V50 with helium varied greatly. One subject remained a non-responder after exercise and the other five were He/O<sub>2</sub> responders after only two or three of the four test runs, and non-responders on the remainder. The lack of consistency of our data, particularly during EIB makes the interpretation of the He/O<sub>2</sub> breathing test less useful than originally claimed.

An increase in maximum expiratory flow rate at the mid vital capacity point (V50) after breathing a low density gas mixture (80% helium, 20% oxygen, He/O<sub>2</sub>) compared to V50 breathing air has been proposed as a method for identifying the major site of airflow obstruction.<sup>1</sup> After breathing He/O<sub>2</sub>, subjects with an increase in V50 greater than 20% have been termed "responders" and this is interpreted as indicating that the major site of resistance to airflow lies in large airways where gas flow is turbulent and density dependent. Those with an increase in V50 less than 20% or with no change have been termed "non-responders" and this indicates that resistance to airflow lies predominantly in small airways where gas flow is laminar and density independent. Response to breathing He/O<sub>2</sub> has been studied in asthmatic subjects after recovery from spontaneous exacerbations,<sup>2</sup> antigen-induced attacks,<sup>3</sup> and exercise-induced bronchospasm<sup>4</sup> (EIB). Recent applications of the technique have attempted

to identify the predominant site of action of anti-cholinergic agents and disodium cromoglycate as a protection for EIB. These have shown different effects dependent on the initial responder status of the subject.<sup>4,5</sup> However, despite wide acceptance of this test as a method of determining the major site of resistance to airflow there are few published data on the reproducibility of response to breathing He/O<sub>2</sub> during EIB. We report studies on 12 asthmatic subjects each of whom performed four identical exercise tests to assess the reproducibility of response to breathing He/O<sub>2</sub> at rest and during EIB and investigate factors that might cause variability in individuals.

## Methods

The subjects were young volunteers whose main symptom was wheezing after exertion. Their personal details together with resting lung function on entry to the study are summarised in table 1. Mean values for forced expiratory volume in one second (FEV<sub>1</sub>), vital capacity (VC), and peak expiratory flow rate

Address for reprint requests: Stephen G Spiro, Department of Respiratory Medicine, Rayne Institute, University College Hospital, London WC1E 6AU.

Table 1 Details of subjects (mean  $\pm$  SEM)

Number	Age (yr)	Male	Female	FEV <sub>1</sub> (l) % predicted	FVC (l) % predicted	PEFR (l/s) % predicted	$\dot{V}_{50}$ (l) % predicted
12	26 (2.4)	7	5	84 (3.8)	95 (2.9)	111 (5.2)	57 (6.4)

(PEFR) were within 20% of predicted but the group mean  $\dot{V}_{50}$  was reduced. None was taking oral corticosteroids, 10 were using aerosol bronchodilators, and seven disodium cromoglycate. All medication was withheld for at least 12 hours before any study. Each exercise test was performed on an automated treadmill for six minutes employing a modification of a standardised protocol.<sup>6</sup> Subjects qualified for the study with an initial screening test to determine the speed and angle of the treadmill belt necessary to produce a heart rate 90% of predicted maximum and to verify that an exercise-induced fall of at least 20% in FEV<sub>1</sub> developed after exercise. Each subject performed four exercise tests at the same time of day at least two days apart employing the speed and incline determined by the screening run. Lung function measurements were obtained from forced VC expirations into a dry wedge spirometer attached to a microprocessor system (Oldelft, "Floop") which also recorded the maximum expired flow volume (MEFV) curve from each VC manoeuvre. Paired expiratory manoeuvres were performed, firstly breathing air, and secondly after breathing the He/O<sub>2</sub> mixture for one minute which was terminated by three VC inspirations then forced expiration into the spirometer. If the VC after breathing the helium mixture was not within 5% of the VC after breathing air it was discarded and the

procedure repeated. Before exercise two or three paired air and helium manoeuvres were recorded but after exercise, since frequent measurements were made to follow the evolution of response of  $\dot{V}_{50}$  to breathing He/O<sub>2</sub>, only a single pair of measurements was made at each time point. Measurements were made at rest, immediately after exercise, and at 3, 5, 10, 15, and 20 minutes. The exercise tests were performed in a centrally heated laboratory with an ambient temperature of 19-21°C, but no attempts were made to control the environment closely.

Analysis of the reproducibility of response to breathing He/O<sub>2</sub> was performed in two stages. Reproducibility at rest was assessed by the percentage change in  $\dot{V}_{50}$  in each subject studied on many occasions. Reproducibility after exercise was assessed by percentage change of  $\dot{V}_{50}$  after He/O<sub>2</sub> at the nadir of  $\dot{V}_{50}$ .

Any effect on response status by breathing He/O<sub>2</sub> for different durations was also studied in a subgroup of the patients who breathed He/O<sub>2</sub> for one minute and three VC breaths, three minutes and three VC breaths, and for only three VC breaths. Predicted normal values were taken from Cotes.<sup>7</sup>

Statistical analysis was performed on the resting data to estimate the variance and to test the homogeneity of the values in order to establish the expected error that could be obtained on any

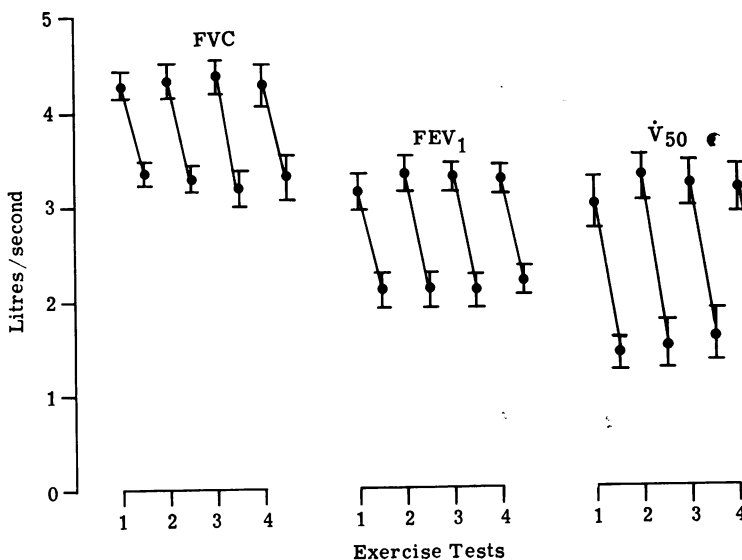


Fig 1 Mean ( $\pm$  SEM) values for FVC, FEV<sub>1</sub>, and  $\dot{V}_{50}$  breathing air for the 12 subjects at rest and the point of lowest  $\dot{V}_{50}$  after exercise for each of the four test runs.

Table 2 Reproducibility of He/O<sub>2</sub> response at rest before four exercise tests

Subject	Number of manoeuvres	Mean $\dot{V}50$ (air) (l/s $\pm$ SD)	% predicted	Mean $\Delta \dot{V}50$ ( $\pm$ SD)	No. $\Delta \dot{V}50 > 20\%$ after He/O <sub>2</sub>
1	8	3.49 (1.0)	64	+ 9.6 (9.14)	1
2	12	4.60 (0.39)	113	- 2.9 (8.64)	0
3	10	2.71 (0.38)	53	+ 5.3 (6.04)	0
4	11	2.79 (0.48)	46	- 4.5 (7.53)	0
5	10	2.54 (0.32)	49	+ 9.1 (6.63)	1
6	8	3.08 (0.53)	61	+ 24.8 (30.88)	7
7	11	3.10 (0.29)	62	+ 5.2 (10.02)	1
8	12	2.06 (0.19)	38	+ 5.1 (14.24)	1
9	12	1.94 (0.57)	39	- 12.1 (11.54)	0
10	12	1.88 (0.29)	34	- 12.2 (7.72)	0
11	12	4.07 (0.42)	79	+ 10.9 (10.31)	3
12	8	3.19 (0.31)	63	- 7.4 (11.29)	0

measurement.

### Results

The group mean values before each of the four exercise tests and mean of the lowest of these measurements after exercise are summarised in fig 1. Before each exercise test lung function for each subject was within 10% of the value obtained before the screening run and the exercise protocol used produced highly reproducible falls in lung function.

#### HELIUM RESPONSIVENESS AT REST

The He/O<sub>2</sub> responses for each subject at rest are summarised in table 2. Only six of the 12 subjects (2, 3, 4, 9, 10, and 12) showed a consistent pattern of response and always had changes of less than 20% for  $\dot{V}50$  after He/O<sub>2</sub> breathing. The other six subjects were less consistent since four showed changes of less than 20% except on one occasion and subject 6 (the only "responder") increased  $\dot{V}50$  by more than 20% on seven of eight occasions. Subject 11 showed

greatest variability with an increase of  $\dot{V}50$  less than 20% on nine occasions but more than 20% on three occasions.

Estimates of the patient variation of the percentage difference in air and He/O<sub>2</sub> flow rates were reasonably homogeneous as confirmed by a Kolmogorov-Smirnov test giving a value for Z of 1.07 ( $p < 0.2$ ). Therefore the overall standard deviation for any observation was estimated by pooling the individual patients' standard deviations giving a resultant value for variation of 12.9%. This must be considered a high value in relation to the defined 20% change between responder and non-responder status.

#### HELIUM RESPONSIVENESS DURING EXERCISE-INDUCED BRONCHOSPASM

Figure 2 shows percentage increase in  $\dot{V}50$  after breathing He/O<sub>2</sub> at the nadir of  $\dot{V}50$  in those six subjects who increased  $\dot{V}50$  consistently by more than 20% after each of four exercises tests. Although these subjects were consistent "responders" the

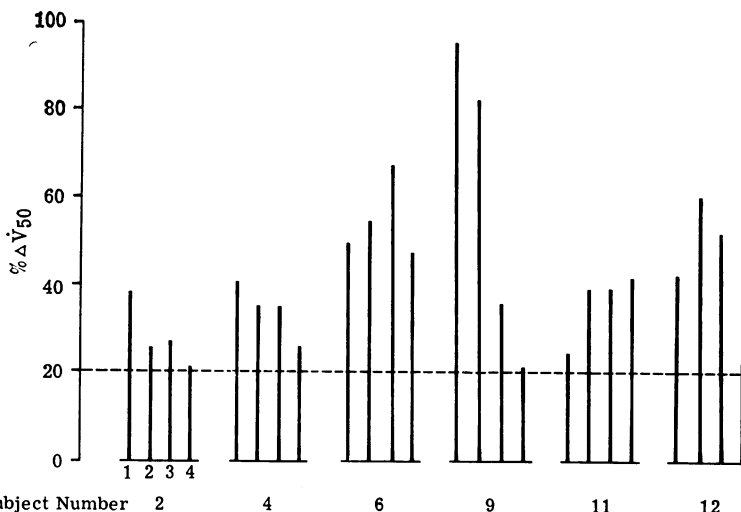


Fig 2 Variation in percentage increase in  $\dot{V}50$  after breathing He/O<sub>2</sub> in each of the six subjects who showed a consistent increase of at least 20% during EIB.

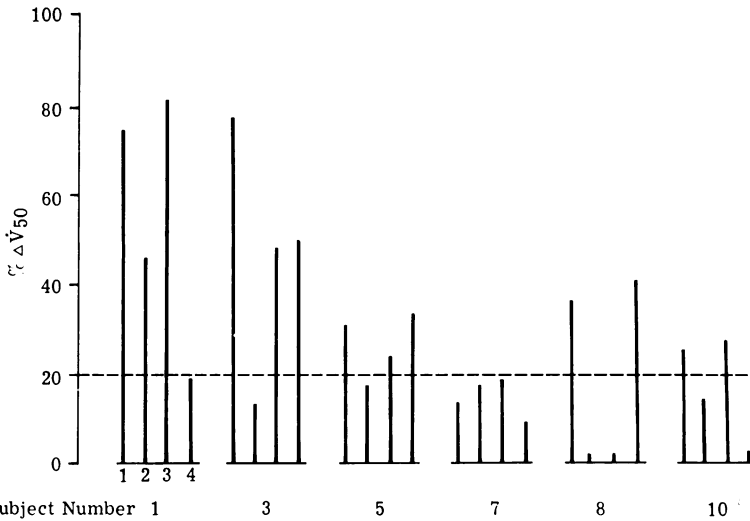


Fig 3 Variation in percentage increase in  $\dot{V}_{50}$  after breathing He/O<sub>2</sub> in each of the six subjects who failed to show an increase of 20% on at least one occasion during EIB.

Table 3 Effect of duration of breathing He/O<sub>2</sub> gas mixtures on responsiveness

Duration of breathing He/O <sub>2</sub>	Subjects at rest				Subjects after exercise				
	1	2	3	4	5	1	2	5	6
3 VC only	+ 6% (2)	+ 19% (2)	- 7% (1)	—	+ 24% (2)	—	—	—	—
1 min + 3 VC	+ 15% (2)	+ 7% (2)	- 8% (1)	+ 10% (2)	+ 35% (2)	+ 12% (1)	- 3% (2)	+ 6% (1)	+ 7% (2)
3 min + 3 VC	- 13% (2)	+ 13% (4)	- 9% (1)	+ 3% (2)	+ 25% (2)	+ 2% (2)	0% (2)	+ 23% (2)	- 9% (2)

( ) Indicate number of studies.

percentage increase in  $\dot{V}_{50}$  after He/O<sub>2</sub> varied widely in some subjects—for example, 9 and 12. The other six subjects were “non-responders” on some occasions and their data are summarised in fig 3. The percentage increase in  $\dot{V}_{50}$  after He/O<sub>2</sub> varied very widely in some of these subjects (1, 3, 8, and 10). One subject (7) failed to show an increase in  $\dot{V}_{50}$  after He/O<sub>2</sub> on each occasion after exercise.

EFFECT OF DURATION OF BREATHING

He/O<sub>2</sub>

Table 3 shows percentage change in  $\dot{V}_{50}$  after breathing He/O<sub>2</sub> for the periods shown at rest or during EIB in six of the subjects. Breathing He/O<sub>2</sub> for three minutes rather than one minute caused no consistent difference to the percentage change in  $\dot{V}_{50}$  for five of the subjects at rest nor during EIB for three of four subjects. The only inconsistency was subject 5 who showed a He/O<sub>2</sub> response after three minutes of breathing He/O<sub>2</sub> but not after breathing it for one minute. Three VC breaths alone at rest in four subjects also showed responses consistent with the measurements made after the longer periods of He/O<sub>2</sub> breathing.

SEVERITY OF OBSTRUCTION AND He/O<sub>2</sub> RESPONSIVENESS

As airways obstruction became more severe ( $\dot{V}_{50}$

lower) the percentage response of  $\dot{V}_{50}$  was more variable. At the lowest levels of  $\dot{V}_{50}$  breathing air the percentage change varied from about 20% to 95% and this occurred in the same subject. There was no relationship between decreasing  $\dot{V}_{50}$  breathing air and the He/O<sub>2</sub> response. Figure 4 shows percentage change in  $\dot{V}_{50}$  after He/O<sub>2</sub> breathing for subjects in whom VC fell by identical amounts from resting values at the nadir of  $\dot{V}_{50}$  after at least two of the four exercise runs. In six subjects when VC fell identically the percentage change in  $\dot{V}_{50}$  after He/O<sub>2</sub> breathing was similar (subjects 2, 5, 7 (twice), and 11 (twice)). In five subjects change in  $\dot{V}_{50}$  varied more widely (6, 3, 1, 8, 9) despite similar (within 3%) changes in VC and in four (1, 5, 8, 10) despite identical changes in VC, the change in  $\dot{V}_{50}$  was so variable as to alter “response” status.

Discussion

Although the He/O<sub>2</sub> breath test has become an accepted method of identifying the major site of airways obstruction, its reproducibility has not been carefully examined. The heterogeneity of responses within groups of asthmatics<sup>2-4,8</sup> with similar resting lung function to those in the present study persuaded us to investigate this.

The He/O<sub>2</sub> response was more variable in the

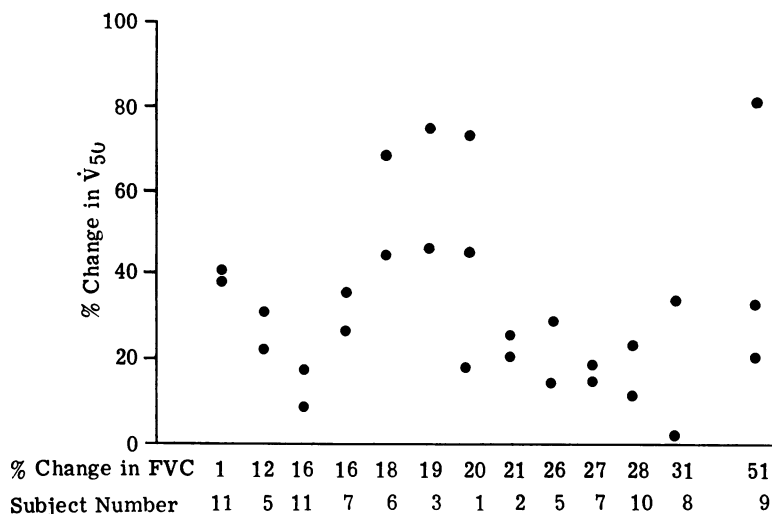


Fig 4 Effect of identical decreases in FVC during EIB in individual subjects on percentage change in  $\dot{V}_{50}$  after breathing He/O<sub>2</sub>.

patients after exercise than at rest. Only seven of the 12 subjects had a consistent response after exercise, including subject 7 who remained a non-responder. However, the percentage change in  $\dot{V}_{50}$  after He/O<sub>2</sub> varied considerably for each individual and widely for these seven subjects as a group (fig 2). In the other five patients the responder status itself was inconsistent with a response of less than 20% on at least one occasion, and twice for two of the subjects (fig 3). The range of percentage change in  $\dot{V}_{50}$  after He/O<sub>2</sub> was also large. Although an increased flow rate of at least 20% after He/O<sub>2</sub> has been suggested as the standard for a "responder" status,<sup>1</sup> this is a somewhat arbitrary definition and others have used different percentage increases.<sup>2</sup> The percentage change after He/O<sub>2</sub> measured in our subjects after exercise was so diverse that any other definition of a "responder" based on larger or smaller increases in  $\dot{V}_{50}$  after He/O<sub>2</sub> would not have changed the inconsistency of our data substantially.

The He/O<sub>2</sub> changes measured at rest were less variable than those after exercise. More pairs of MEFV curves were available at rest as at least two pairs were performed before each period of exercise. Only six patients showed consistency and were non-responders after each pair of curves. There was a change in response status on at least one occasion for each of the other six patients. However, the response status was reasonably reproducible as four of the six patients who showed a change in status did so only once in eight to 12 measurements (table 2), and the actual percentage change in  $\dot{V}_{50}$  after He/O<sub>2</sub> was much smaller than during EIB.

The reasons for the majority of our patients being He/O<sub>2</sub> non-responders at rest is not obvious although

their low resting  $\dot{V}_{50}$  is suggestive of predominant small airways obstruction, but it is an observation at variance with other studies where the majority of mild asthmatics were responders.<sup>1-3</sup> The increase in responder status and percentage increase in  $\dot{V}_{50}$  with He/O<sub>2</sub> after exercise has been previously noted.<sup>1,4,8</sup> However, the reported association of decreasing He/O<sub>2</sub> response with increasing severity of airways obstruction<sup>2</sup> was not noted in this study, nor in other reports.<sup>1,9</sup> The period breathing He/O<sub>2</sub> has varied from two to 10 minutes in other patient studies,<sup>3,8,9</sup> and was confined to only three VC manoeuvres in a study of normal subjects.<sup>10</sup> As we intended to make frequent measurements after exercise in order to measure the He/O<sub>2</sub> response at the nadir of EIB, we chose a breathing period of one minute. There was no evidence from other studies that the duration of He/O<sub>2</sub> breathing appeared critical to the development of the response but all studies have included three VC manoeuvres. We observed no differences in the responses of a subgroup of patients tested at rest and the result was similar for three of four subjects after exercise (table 3).

Another possible cause of the present measurements differing from other reports was that the MEFV curves were measured with a spirometer rather than a plethysmograph. However, the possible differences in flow rates because of gas compressibility which affect measurements made within a plethysmograph have already been systematically studied and were shown to alter the He/O<sub>2</sub> response status in only one of 31 patients with asthma.<sup>2</sup> Since spirometry only was used, changes in total lung capacity or residual volume after exercise could not be measured.

However, this study was confined to reporting changes with He/O<sub>2</sub> in pairs of matched MEFV curves at rest and after exercise, and not changes in flow rates between rest and exercise, as in the latter knowledge of lung volume changes become important. There is no information on the consistency of lung volume changes after repeated episodes of EIB. In our patients the percentage fall in FEV<sub>1</sub> and PEFV for each subject was very consistent and in 10 subjects the drop in VC at the lowest V50 was identical after at least two tests. It could be assumed that where VC changes were identical with similar falls in FEV<sub>1</sub>, the lung volume changes should also be similar. Even in these tests the change in V50 after He/O<sub>2</sub> showed considerable variability and was unrelated to the decrease in VC (fig 4). Thus it appears that the intrasubject variation with He/O<sub>2</sub> after exercise was not caused by differences in lung volume.

The measurements of changes in the MEFV curve after He/O<sub>2</sub> seemed unreliable in normal subjects<sup>10</sup> and He/O<sub>2</sub> response has been shown to correlate poorly with airways resistance.<sup>8</sup> The He/O<sub>2</sub> response test is either too inconsistent to differentiate large from small airways obstruction reliably in EIB, or the patients themselves may vary so much that the interpretation of the He/O<sub>2</sub> test is far more complex than originally proposed.

This work was supported in part by Janssen Pharmaceutical Limited. We are grateful for the advice

given by Dr S Freedman, and for the help of Mr A Cobley and Miss Angela Betchley.

#### References

- <sup>1</sup> Despas PJ, Leroux M, Macklem PT. Site of airway obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium/oxygen mixture. *J Clin Invest* 1972;**51**:3235-43.
- <sup>2</sup> Benatar SR, Clark TJH, Cochrane GM. Clinical response to low density gas breathing in asthmatics. *Am Rev Respir Dis* 1975;**111**:126-34.
- <sup>3</sup> Cheng Yeung M, Abboud R, Tsao MS, Maclean L. Effect of helium on maximal expiratory flow in patients with asthma before and during induced bronchoconstriction. *Am Rev Respir Dis* 1976;**113**:433-43.
- <sup>4</sup> McFadden ER Jr, Ingram RH Jr, Haynes RL, Wellman JJ. Predominant site of flow limitation and mechanisms of post exertional asthma. *J Appl Physiol: Respirat Environ Exercise Physiol* 1977;**42**:746-52.
- <sup>5</sup> Thomson NC, Patel KR, Kerr JW. Sodium cromoglycate and ipratropium bromide in exercise-induced asthma. *Thorax* 1978;**33**:694-9.
- <sup>6</sup> Eggleston P, Guerrant JL. A standardized method of evaluating exercise-induced asthma. *J Allerg Clin Immunol* 1976;**58**:414-25.
- <sup>7</sup> Cotes JE. *Lung function. Assessment and application in medicine*. Fourth edition. Oxford: Blackwell, 1979.
- <sup>8</sup> Mildon A, Leroux M, Hutcheon M, Zamel N. The site of airways obstruction in exercise-induced asthma. *Am Rev Respir Dis* 1974;**110**:409-14.
- <sup>9</sup> Antic R, Macklem PT. The influence of clinical factors on site of airways obstruction in asthma. *Am Rev Respir Dis* 1976;**114**:851-60.
- <sup>10</sup> Macdonald JB, Cole TJ. The flow-volume loop: reproducibility of air and helium-based tests in normal subjects. *Thorax* 1980;**35**:64-9.