

Asthma—The Physiological and Clinical Spectrum in Childhood

Respiratory Function Studies in its Assessment

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Hill, D. J., Landau, L. I., McNicol, K. N., and Phelan, P. D. (1972). *Archives of Disease in Childhood*, **47**, 874. **Asthma—the physiological and clinical spectrum in childhood: respiratory function studies in its assessment.** Tests of respiratory function based on spirometry have hitherto proved of limited value in the assessment of asthmatic children in the interval phase. In an attempt to provide more information on this subject, respiratory function studies using a body plethysmograph were carried out in 106 asthmatic children aged 13 to 15 years during an asymptomatic period. The children were selected to cover the whole spectrum of asthma in childhood; they were divided into 4 grades on clinical criteria, and the results of the physiological studies compared with the clinical gradings.

Results indicated that *maximum expiratory flow volume* curves, when combined with an estimation of lung volumes, provided the best assessment of the severity of a child's asthma.

Using this test of respiratory function, most children in whom asthma had been a trivial complaint had virtually no abnormality, but a small number had mild airways obstruction. Those with chronic continuing asthma had evidence of severe airways obstruction and pulmonary hyperinflation. In children with episodic asthma, the degree of abnormality was variable and the frequency of the attacks seemed to be a major factor in determining this.

It is concluded that respiratory function studies are a valuable tool in evaluating asthma in childhood, particularly when the clinical history is difficult to assess.

Respiratory function tests are being used increasingly in the assessment of asthma to provide objective evidence of the severity of the disease and of the response to treatment. The degree of airways obstruction in asthma varies from time to time, and it has been suggested that frequent and repeated measurements are necessary to indicate the severity of the disease.

Previous studies have produced conflicting reports concerning the persistence of abnormalities in respiratory function in asymptomatic asthmatic children. Kraepelien, Engstrom, and Karlberg (1958) found persistent hyperinflation during asymptomatic periods, the changes being more marked in children with frequent episodes. In a subsequent study, Kraepelien (1959) found that the hyperinflation did eventually disappear in the

absence of recurring episodes. Andrews and Simmons (1959) also found raised residual volume and functional residual capacity in moderate and severe asthmatics during symptom-free periods. However, Orzalesi, Cook, and Hart (1964) found an increased residual volume in only 3 of 29 asymptomatic asthmatics. Engstrom *et al.* (1959) found a reduced ratio of forced expiratory volume to vital capacity during symptom-free periods, and again the reduction was more marked in the child with frequent episodes. However, in another study, the same group (Engstrom and Karlberg, 1962) found the ratio reduced in only 6 of 44 asymptomatic children. Weng and Levison (1969) in a study of asthmatic children during an asymptomatic period, found forced expiratory volume in one second was within normal limits but maximal midexpiratory flow was reduced.

Assessment of the significance of these reports

has been difficult as the samples studied have not been randomly chosen, and there was no clear definition of the clinical status of the patients studied. Consequently it has been difficult to compare different studies and to draw any conclusions about the value of respiratory function studies in an asymptomatic asthmatic or about the relation of the findings to the probable severity of the disease.

Most of these studies have been based on simple spirometric measurements of vital capacity and forced expiratory volume and measurements of lung volumes by gas dilution. Forced expiratory volume and peak expiratory flow are not the most satisfactory tests of airways obstruction as they are partially dependent on patient effort and co-operation, and are affected more by alterations in the larger than in the smaller airways (Mead *et al.*, 1967). In asthma, the major pathological changes are in the medium and smaller airways (Messer, Peters, and Bennett, 1960). Maximum expiratory flow volume curves have been suggested as a more satisfactory test of airways obstruction because they reflect directly narrowing of the smaller airways (Mead *et al.*, 1967). Gas dilution methods may underestimate lung volumes in the presence of airways obstruction because of trapped air (Meisner and Hugh-Jones, 1968). For this reason, measurements using a body plethysmograph are preferred as these estimate total intrathoracic gas volumes (Du Bois *et al.*, 1956).

The present investigation was undertaken to attempt to define more accurately the range of abnormality in several parameters of respiratory function in asthmatic children during a symptom-free stage, so that the best test could be determined. The patients studied were drawn from children taking part in a long-term epidemiological survey and the clinical severity of the asthma was carefully defined. In this way it was hoped to provide information that would aid the interpretation of respiratory function results in asthmatic children referred for assessment.

Materials

The 106 children studied were from 397 asthmatic children who, with 82 controls, have been the subject of a longitudinal study. This epidemiological study has involved a detailed follow-up of two random samples from the Melbourne community. The samples were obtained at 7 and 10 years of age, respectively, both groups being followed to 14 years of age. The group sampled at 10 years contained a larger number of more severely affected asthmatic children. The methods of sampling in these two phases have been described previously (Williams and McNicol, 1969; McNicol, Williams, and Gillam, 1970). The sampling ensured a balanced representation of patients with varying

grades of asthma from the various social and geographic divisions of the Melbourne population.

The children were studied when symptomatically well—designated as *interval phase* for the purpose of this study. There were 31 girls and 75 boys whose ages ranged from 13 to 15 years. Lung function tests were done on the day they attended for final assessment at approximately 14 years of age. Tests were done on one occasion only and 8 children unable to perform the manoeuvres satisfactorily were excluded from the study. The tests were performed in the autumn and winter months of the year; most studies were performed between 10 a.m. and 12 midday. 30% of children with continuing asthma were on oral or inhalation bronchodilator therapy at the time of the study, but these had not been used for at least 3 hours before the tests. 10 children with chronic asthma were on low dose corticosteroids.

Methods

Clinical assessment. This was assigned independently (K. McN.) on the basis of history and clinical findings at the 14-years-of-age examination as part of the epidemiological study previously mentioned. 4 groups were defined.

Grade A. Children who had 5 or less episodes of wheezing by 14 years of age. Most of these children had no attacks after 7 or 8 years of age.

Grade B. Children with a continuing history of episodic asthma over 3 to 5 years, but who had not wheezed in the 12 months before examination at 14 years. Most had ceased to wheeze by 10 years of age.

Grade C. Children with a long-standing history of episodic asthma and who had wheezed in the 12 months before study. Most of these children had several episodes each year since infancy.

Grade D. Children with a long-standing history with evidence of chronic unremitting asthma in the 12 months before examination. They had had periods of persistent asthma in the preceding year, or their longest symptom-free period in that time was less than 1 month. 60% of these children showed clinical evidence of pulmonary hyperinflation—barrel chest or pigeon chest deformity. In 75% of them rhonchi were audible after coughing and deep breathing when examined in an interval phase.

The detailed analyses of the children obtained during the period of the epidemiological study provided clinical details not usually available to a physician. All the results of the clinical assessment were not available until the classification of laboratory data had been completed.

Spirometry. A Godart expirograph was used to measure vital capacity (VC) and forced expiratory volume in one second (FEV₁). The best of three measurements was taken.

Body plethysmography. An air-conditioned flow-displacement body plethysmograph (J. Mead, personal communication 1970), was used to measure lung volumes.

Thoracic gas volume (TGV) was measured by applying Boyle's law (Du Bois *et al.*, 1956), and total lung capacity (TLC) and residual volume (RV) determined. The mean of 3 or 4 satisfactory recordings was obtained.

Maximum expiratory flow volume (MEFV) curves are obtained by simultaneously recording maximum expiratory flow and expired lung volume during a forced expiration from TLC to RV. During such a forced expiration, peak flow occurs just below TLC, and the maximum expiratory flow rate progressively falls with decreasing lung volume to zero at RV. MEFV curves show the relation between maximum expiratory flow and the lung volume at which the flow was obtained. Maximum expiratory flow rates are determined by airways resistance and lung volume (Mead *et al.*, 1967).

In this study, maximum expiratory flow was measured at the mouth using a Fleisch No. 4 pneumotachograph and expired lung volume in the body plethysmograph, and these were displayed in the y and x axes, respectively, of a storage oscilloscope and the curve obtained. The procedure was repeated until it was certain that the child was making a maximum effort which could be determined by the reproducibility of the curve.

To quantitate the MEFV curve, maximum expiratory flow can be measured after various percentages of the TLC have been expired. In this study, maximum expiratory flow was measured from the curve after 50% of the TLC had been expired. Maximum expiratory flow varies with lung size and, to allow for this, flow is divided by TLC and expressed as a fraction of TLC per second (Zapletal *et al.*, 1969).

An MEFV curve from a normal subject is shown in Fig. 1. After about 20% of TLC has been expired, the curve is effort-independent, that is, once maximum flow is achieved increasing effort will not lead to an increase in flow (Mead *et al.*, 1967).

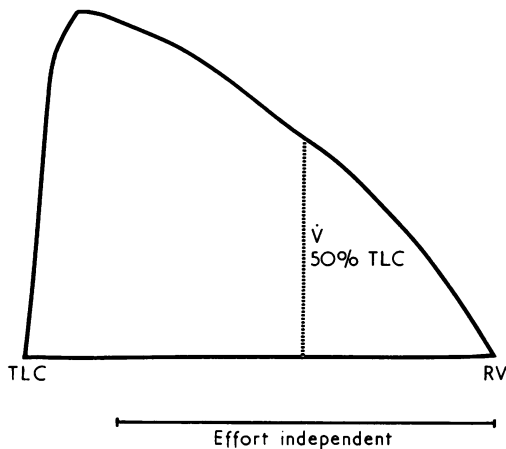


FIG. 1.—Maximum expiratory flow volume curve from a normal subject. Maximum expiratory flow is recorded on the y axis (vertical) and expired volume on the x axis (horizontal). Maximum expiratory flow is effort-independent after about 20% of the TLC has been expired.

Isoprenaline 1%, was given to all subjects by inhalation for 3 minutes to confirm the presence of reversible airways obstruction; detailed results of this response will not be reported here.

Normal Data

Normal data used in this study were obtained from 4 sources. The static and dynamic lung volumes were derived from the reports of Cook and Hamann (1961) and Murray and Cook (1963). These authors gave regression equations relating lung volumes to height. Normal limits were taken as 80% to 120% of predicted. Polgar and Promadhat (1971) derived graphs for lung volumes related to height from data reported by a number of authors. Analysis of their graphs for the mean predicted values and 2 SD about the mean indicated that 2 SD were about 20% of the mean. In a routine laboratory, the use of normal values extending from 80% to 120% of predicted is more practical than individual derivations from regression equations. The values for RV/TLC ratio were based on those given by Polgar and Promadhat (1971), mean being 21% and 2 SD above the mean 30%. The lower limit of FEV₁/VC ratio was taken as 72% (Polgar and Promadhat, 1971). Zapletal *et al.* (1969) reported normal values for maximum expiratory flow derived from MEFV curves. Based on these data, maximum expiratory flow at 50% TLC was considered abnormal at 0.4 TLC/sec and below. 15 normal children of similar age to the subjects reported here were studied during this investigation to confirm these normal values.

Results

In Table I the distribution of the 106 children among the 4 clinical grades is shown. The relatively high number of children in grades C and D are the result of deliberately studying the more severely affected asthmatic children.

TABLE I
Distribution of Children in 4 Clinical Grades

Grade				Number
A	14
B	15
C	39
D	38

The results of the spirometric measurements are given in Table II. In Fig. 2 the subjects are grouped according to both clinical status and FEV₁/VC, values below 72% being abnormal. FEV₁/VC showed some correlation with the clinical severity of the asthma, the majority of children in grade D being abnormal. However, only some children in grade C were abnormal and none in grades A and B. Relating FEV₁ to predic-

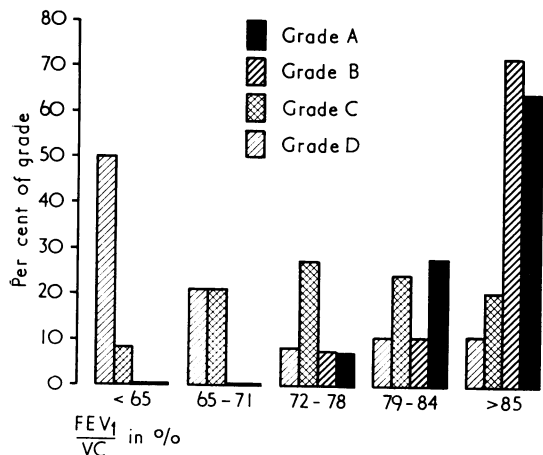


FIG. 2.—Children in each clinical grade (A to D) grouped according to the ratio FEV₁ to VC.

ted normal gave similar results. Consequently, spirometry seemed to detect only children with severe airways obstruction.

Abnormalities in MEFV curves were assessed in two ways. A normal subject has a curve that is concave or straight to the x (volume) axis (Fig. 1). With progressively increasing airways obstruction, there is increasing convexity towards the x axis (Fig. 3). In Table III the shape of the MEFV curves is correlated with the clinical findings. Maximum expiratory flow at 50% TLC was measured directly from the MEFV curves and the number of children in each clinical grade with airways obstruction, as indicated by abnormal flows (below 0.41 TLC/sec), is shown also in Table III. Maximum expiratory flows in relation to the clinical grade is shown diagrammatically in Fig. 4. There was generally a good correlation between the clinical gradings and maximum expiratory flows. All but 1 child from grade A had normal flows and in most of grade D they were abnormally low. There was a wide scatter in grade C and to a lesser extent in grade B. 17

TABLE II
Spirometric Measurements: Number of Children in Each Grade with Abnormal Results are Given Together with Percentage of Children in Grade They Represent

Grade	FEV ₁ /VC <72%		FEV ₁ /(FEV ₁ Predicted) <80%	
	No.	%	No.	%
A	0	—	0	—
B	0	—	0	—
C	11	29	6	16
D	27	71	23	61

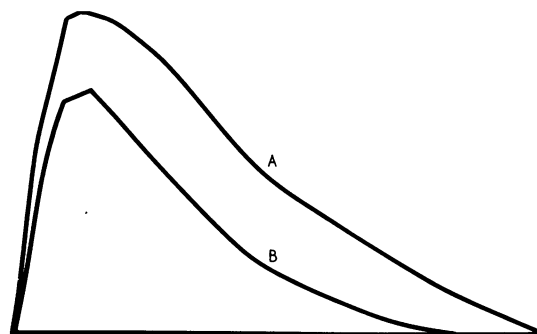


FIG. 3.—An MEFV curve from a mild to moderate asthmatic (curve A) and from a severe asthmatic (curve B). Compare Fig. 1.

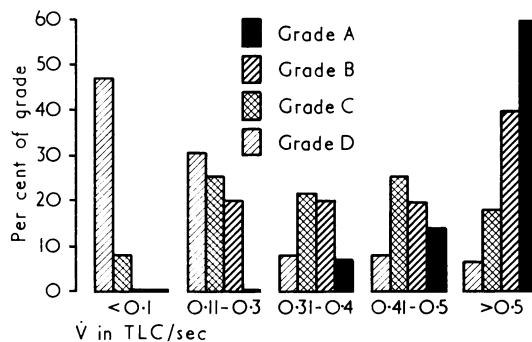


FIG. 4.—Children in each clinical grade (A to D) grouped according to maximum expiratory flow (max) \dot{V} at 50% TLC.

TABLE III

Maximum Expiratory Flow Volumes: Number of Children with Abnormal Results in Each Grade are Given

Grade	Shape of MEFV Curves			Maximum Expiratory Flow at 50% TLC <0.41 TLC/sec
	Concave	Straight	Convex	
A	5 (36%)	8 (57%)	1 (7%)	1 (7%)
B	3 (20%)	8 (53%)	4 (27%)	4 (27%)
C	4 (10%)	12 (30%)	23 (69%)	18 (46%)
D	2 (5%)	8 (21%)	28 (74%)	32 (84%)

TABLE IV

Static Lung Volumes: Number of Children in Each Grade with Abnormal Results are Given

Grade	VC/VC (Predicted) <80%	TLC/TLC (Predicted) >120%	RV/RV (Predicted) >120%	RV/TLC >30%
A	0 —	0 —	3 (21%)	1 (7%)
B	0 —	2 13%	5 (33%)	4 (27%)
C	2 (5%)	13 33%	13 (33%)	9 (23%)
D	1 (1%)	12 32%	31 (82%)	20 (52%)

children with a normal FEV₁/VC had abnormally low maximum expiratory flows and the relation between the two parameters is shown in Fig. 5. Thus, in these 17 children airways obstruction was present but not detected by spirometry.

In Table IV, the children in each grade with abnormalities in TLC, VC, RV, and RV/TLC are shown. VC was normal in virtually all the children studied. TLC was increased in one-third of children in grades C and D. Hyperinflation was marked in children in grade D as indicated by an increased RV/TLC. This is probably a better indication of persistent hyperinflation due to airways obstruction than an absolute increase in RV over predicted normal. A large RV may be the result of large lungs which seemed to be present in some children in grades B, C, and D. The large lungs

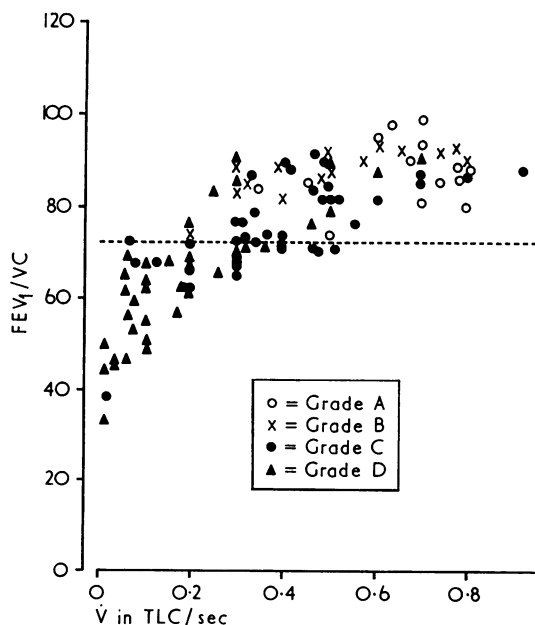


FIG. 5.—The relation between FEV₁/VC and maximum expiratory flow (\dot{V} max). The lower limit of normal for FEV₁/VC is indicated by the broken line.

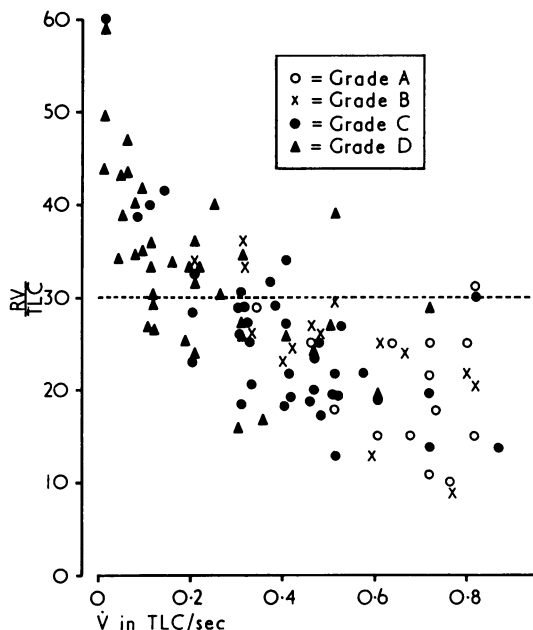


FIG. 6.—The relation between RV/TLC and maximum expiratory flow (\dot{V} max) at 50% TLC. The upper limit of normal for RV/TLC is indicated by the broken line.

in some asthmatic children may be the result of recurrent asthma, as it has been shown that TLC increases markedly during acute episodes (Woolcock and Read, 1966). The relation between RV/TLC and maximum expiratory flow is shown in Fig. 6. It will be seen that there was a good correlation between hyperinflation and airways obstruction. All but 2 patients with RV/TLC greater than 30% had a maximum expiratory flow of 0.41 TLC/sec or less.

Discussion

The results of this study show clearly that there is a gradation in abnormalities of respiratory function in children with asthma during asymptomatic periods, and that the degree of abnormality correlates with the clinical severity of the disease.

If the asthma had been trivial (grade A), no persisting abnormalities could be detected. A few children with asthma lasting 3 to 5 years but symptom free for the 12 months before study (grade B) had minor abnormalities in maximum expiratory flow and in residual volume. With increasing frequency of asthmatic episodes (grade C), there was a higher incidence of low maximum expiratory flows and of hyperinflation. The majority of children defined as chronic asthmatics (grade D) had abnormally low maximum expiratory flows and hyperinflation. The conflicting reports of previous workers who had studied asthmatic children during symptom-free periods can be explained from this study, in that the disturbances they described in their interval-phase asthmatics reflect the spectrum of the severity of this disease.

There can be considerable difficulty in assessing the severity of asthma on a clinical history. Some parents will overestimate the problem, others underestimate it. This in part may explain the few children in whom the clinical grading did not correlate with the test findings.

The study indicated that spirometric tests were of limited value in assessment of asthmatic children during a symptom-free period. FEV_1 was abnormal only in children with severe chronic asthma and failed to detect persistent airways obstruction during symptom-free periods in those with episodic asthma (Table II). FEV_1 is less affected by flows low in the VC than those high in the VC. Obstruction in the smaller airways primarily affects flow low in the VC (Mead *et al.*, 1967). Therefore, it is not surprising that FEV_1 was not particularly useful as persisting abnormalities in asthma probably are in the smaller airways (Woolcock, Vincent, and Macklem, 1969).

MEFV curves seemed to provide the most useful information concerning persisting airways obstruction in asthma and they appeared to be more sensitive than FEV_1 . The degree of convexity of the curve to the volume (x) axis and measurement of maximum expiratory flow at 50% TLC were good indices of the severity of the airways obstruction. If there was no convexity, significant asthma was highly unlikely. Maximum expiratory flow at 50% TLC indicated the degree of obstruction and showed a good correlation with the clinical severity of the asthma and with the magnitude of the hyperinflation (Fig. 4, 6).

These results support the findings of Zapletal *et al.* (1971) who used MEFV curves to assess airways obstruction in asthma and cystic fibrosis and found maximum expiratory flow at 25% VC (equivalent to about 40% TLC in normal adoles-

cents) to be the most sensitive index of airways obstruction. In the present study flow was measured at a fixed percentage of TLC rather than of VC, as maximum expiratory flow at a given lung volume is dependent on the static recoil pressure at that volume (Mead *et al.*, 1967). Therefore, it seemed more logical to take a fixed point in the TLC at which to compare expiratory flows rather than a fixed percentage of the VC. A fixed percentage of VC may represent quite different absolute lung volumes depending on the size of RV. Weng and Levison (1969) suggested that maximum midexpiratory flow calculated from the spirogram was a useful index of persisting airways obstruction, but, in a subsequent study, Levison *et al.* (1970) found that maximum expiratory flow at 50% VC was more sensitive.

The persisting abnormalities in maximum expiratory flow and in RV/TLC were almost certainly the result of continuing airways obstruction. The increased RV/TLC probably results from closure of the narrowed airways at a higher than usual lung volume. There is virtually no evidence that destructive emphysema as distinct from hyperinflation develops as a consequence of long-standing asthma in childhood (Gold, Kaufman, and Nadel, 1967).

Within the clinically defined grades, there was considerable variation in the severity of the detected abnormalities. This is to be expected as the degree of bronchial obstruction may vary from day to day and even during the same day. The range of abnormality was widest in children in grade C, who were the continuing episodic asthmatics. It was difficult to define clearly the actual frequency of episodes in some children in this group. Those with the more marked abnormalities had had asthma more recently, which in itself tended to indicate more frequent episodes. It should be remembered that the changes detected in these asymptomatic children were qualitatively similar, though less marked, to those reported during acute exacerbations of asthma (Weng and Levison, 1969). A number of children in grade D were seen within a few days of an episode of overt wheezing, and it is known that physiological changes occurring with acute asthma may take some days to resolve (Engstrom, 1964). However, the changes detected in these children were probably a reflection of the normal state of their lower airways, as they were never free of asthma for a prolonged period. The fact that the changes in the children in grade D were so uniform supports this conclusion.

From the data obtained in this study, it is possible to make certain predictions that should help the

interpretation of respiratory function measurements in asymptomatic asthmatic children. If a child with a history of asthma has a maximum expiratory flow at 50% TLC greater than 0.5 TLC/sec, it is likely that he has no more than mild episodic asthma or has ceased to wheeze. Maximum expiratory flow at 50% TLC below 0.2 TLC/sec, particularly if combined with hyperinflation, is an indication of severe asthma. Measurements between 0.2 TLC/sec and 0.5 TLC/sec are difficult to interpret, and in children with these results repeated MEFV curves and estimations of lung volumes are probably necessary to indicate the severity of the asthma. In these children the measurement of bronchial lability (Jones, 1966) may also help to identify the severity of the asthma.

The equipment used to obtain the MEFV curves was complex and not readily available in a routine laboratory. A simple direct-writing machine for recording MEFV curves has been designed (Peters, Mead, and Van Ganse, 1969), but it does not seem to have received wide acceptance. One of its major disadvantages is that it records expired volume which may be quite different from true lung volume in severe airways obstruction because of the gas compression that occurs (Takisima *et al.*, 1967). The great advantage of the body plethysmograph is that true lung volume is measured during a forced expiration. Furthermore, calculation of RV and TLC is rapid in the plethysmograph, and trapped air is measured, which may not be the case with helium dilution methods when there is severe airways obstruction (Meisner and Hugh-Jones, 1968). Flow displacement body plethysmographs have distinct advantages over pressure and volume displacement types, especially in ease and cost of construction, and are likely to become more widely available for routine use. It is important that they do so, because MEFV curves, combined with measurements of lung volume, appear to be the most satisfactory test for airways obstruction and should be within the capacity of most routine respiratory laboratories.

MEFV curves do seem to provide useful information in the assessment of asthma in childhood. They are certainly of value in the identification of children with chronic severe or with very mild asthma. While children with severe chronic asthma can usually be identified clinically, in some this may not occur due to varying parental attitudes to the disease, inability to wheeze loudly because of severe limitation of maximum expiratory flow, or modification of physical activity as a result of breathlessness. The tests recommended here will

detect the children with chronic asthma and will also provide a basis for assessing the efficacy of therapy. In the child with episodic asthma, the value of the tests is less clear but they do detect persistent airways obstruction in a significant number. Repeated tests would probably provide additional information. Random tests in episodic asthmatics are of limited value because of the rapid changes in the results which can occur over short periods and this applies particularly to spirometric measurements which detect only severe obstruction. MEFV curves, because of their increased sensitivity, may well provide more reliable information in this group of patients.

REFERENCES

- Andrews, J. F., and Simmons, D. H. (1959). Lung volumes of normal and asthmatic children. *Pediatrics*, **23**, 507.
- Cook, C. D., and Hamann, J. F. (1961). Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years. *Journal of Pediatrics*, **59**, 710.
- Du Bois, A. B., Botelho, S. Y., Bedell, G. N., Marshall, R., and Comroe, J. H. (1956). Rapid plethysmographic method for measuring thoracic gas volume. A comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *Journal of Clinical Investigation*, **35**, 322.
- Engstrom, I. (1964). Respiratory studies in children. XI. Mechanics of breathing, lung volumes and ventilatory capacity in asthmatic children from attack to symptom-free status. *Acta Paediatrica Suppl.* **155**, 1.
- Engstrom, I., Escardo, F. E., Karlberg, P., and Kraepelien, S. (1959). Respiratory studies in children. VI. Timed vital capacity in healthy children and in symptom-free asthmatic children. *Acta Paediatrica*, **48**, 114.
- Engstrom, I., and Karlberg, P. (1962). Respiratory studies in children. X. Lung volumes in relation to ventilatory capacity and mechanical properties of the lungs in symptom free asthmatic children. *Acta Paediatrica*, **51**, 529.
- Gold, W. M., Kaufman, H. S., and Nadel, J. A. (1967). Elastic recoil of the lungs in chronic asthmatic patients before and after therapy. *Journal of Applied Physiology*, **23**, 433.
- Jones, R. S. (1966). Assessment of respiratory function in the asthmatic child. *British Medical Journal*, **2**, 972.
- Kraepelien, S. (1959). Respiratory studies in children. VII. A longitudinal study of the lung volumes in asthmatic children during symptom-free periods. *Acta Paediatrica*, **48**, 335.
- Kraepelien, S., Engstrom, I., and Karlberg, P. (1958). Respiratory studies in children. II. Lung volumes in symptom-free asthmatic children, 6-14 years of age. *Acta Paediatrica*, **47**, 399.
- Levison, H., Kamel, M., Weng, T. R., and Kruger, K. (1970). Expiratory flow rates determined by wedge and water spirometer in children and young adults. *Acta Paediatrica Scandinavica*, **59**, 648.
- McNicol, K. N., Williams, H. E., and Gillam, G. L. (1970). Chest deformity, residual airways obstruction and hyperinflation, and growth in children with asthma. I. Prevalence findings from an epidemiological study. *Archives of Disease in Childhood*, **45**, 783.
- Mead, J., Turner, J. M., Macklem, P. T., and Little, J. B. (1967). Significance of the relationship between lung recoil and maximum expiratory flow. *Journal of Applied Physiology*, **22**, 95.
- Meisner, P., and Hugh-Jones, P. (1968). Pulmonary function in bronchial asthma. *British Medical Journal*, **1**, 470.
- Messer, J. W., Peters, G. A., and Bennett, W. A. (1960). Causes of death and pathological findings in 304 cases of bronchial asthma. *Diseases of the Chest*, **38**, 616.
- Murray, A. B., and Cook, C. D. (1963). Measurement of peak expiratory flow rates in 220 normal children from 4.5 to 18.5 years of age. *Journal of Pediatrics*, **62**, 186.
- Orzalesi, M. M., Cook, C. D., and Hart, M. C. (1964). Pulmonary function in symptom-free asthmatic patients. *Acta Paediatrica*, **53**, 401.

- Peters, J. M., Mead, J., and Van Ganse, W. F. (1969). A simple flow-volume device for measuring ventilatory function in the field. *American Review of Respiratory Diseases*, **99**, 617.
- Polgar, G., and Promadhat, V. (1971). *Pulmonary Function Testing in Children*. Saunders, Philadelphia and London.
- Takishima, T., Grimby, G., Graham, W., Knudson, R., Macklem, P. T., and Mead, J. (1967). Flow-volume curves during quiet breathing, maximum voluntary ventilation, and forced vital capacities in patients with chronic lung disease. *Scandinavian Journal of Respiratory Diseases*, **48**, 384.
- Weng, T. R., and Levison, H. (1969). Pulmonary function in children with asthma at acute attack and symptom-free status. *American Review of Respiratory Diseases*, **99**, 719.
- Williams, H., and McNicol, K. N. (1969). Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *British Medical Journal*, **4**, 321.
- Woolcock, A. J., and Read, J. (1966). Lung volumes in exacerbations of asthma. *American Journal of Medicine*, **41**, 259.
- Woolcock, A. J., Vincent, N. J., and Macklem, P. T. (1969). Frequency dependence of compliance as a test for obstruction in the small airways. *Journal of Clinical Investigation*, **48**, 1097.
- Zapletal, A., Motoyama, E. K., Gibson, L. E., and Bouhuys, A. (1971). Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics*, **48**, 64.
- Zapletal, A., Motoyama, E. K., Van de Woestijne, K. P., Hunt, V. R., and Bouhuys, A. (1969). Maximum expiratory flow-volume curves and airway conductance in children and adolescents. *Journal of Applied Physiology*, **26**, 308.

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