Abnormalities of lung function in hay fever¹

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Morgan, E. J. and Hall, D. R. (1976). *Thorax*, 31, 80-86. **Abnormalities of lung function in hay fever.** Twenty subjects with symptoms of hay fever were studied to see whether abnormalities could be detected in the function of small airways. The investigations included dynamic compliance at varying respiratory frequencies, closing capacity, residual volume, transfer factor, and maximal expiratory flow-volume curves. The tests were repeated in the winter when symptoms had resolved.

Frequency dependence of compliance was found in eight subjects with symptoms (40%), closing capacities being abnormal in only two instances. Conventional pulmonary function tests, including expiratory flow rates at mid vital capacity, were within the predicted range for all subjects. When tests were repeated in the winter, frequency dependence of compliance was no longer present in subjects whose symptoms had resolved.

The study suggests that reversible small airway abnormalities are present in a significant proportion of subjects with symptoms of hay fever and that such abnormalities are best detected by the measurement of dynamic compliance at varying respiratory frequencies.

Patients with bronchial asthma frequently admit to previous attacks of hay fever, and bouts of wheezing commonly occur in patients with severe hay fever. In both hay fever and asthma the inhalation of pollen results in a type I hypersensitivity reaction with similar pathological changes in the nasal and bronchial mucosa respectively.

Previous investigators (Vondra *et al.*, 1971; Ionescu, 1973; Grossman and Putnam, 1975) have shown that bronchoconstriction may be induced in subjects with hay fever by the administration of acetylcholine or methacholine, a significant fall in one-second forced expiratory volume (FEV₁) and maximal mid expiratory flow (MMF) occurring in 20 to 50% of cases. Conventional tests of lung function in patients with hay fever are usually normal (May and Kotowska, 1965). Recent studies have shown, however, that significant obstruction may exist in the peripheral airways even when these conventional tests are normal (Macklem, 1972). In symptom-free asthmatics with normal routine lung function tests the presence of persistent small airways obstruction has been sug-

gested by the finding of reduced maximal expiratory flows at low lung volumes (Hill, Landau, and Phelan, 1972), elevated closing volumes (CV) (McCarthy and Milic-Emili, 1973), and frequency dependence of dynamic compliance (C_{dyn}) (Woolcock, Vincent, and Macklem, 1969; Levine *et al.*, 1970; Hill *et al.*, 1972).

In order to determine whether there are similar abnormalities of small airways function in subjects with hay fever, a group of volunteers with hay fever but without an antecedent history of asthma or wheezing was studied while they had symptoms in the summer or autumn and again when the symptoms had resolved in the winter.

MATERIAL AND METHODS

Twenty subjects were selected from the West Virginia University student population and from the University Hospital Allergy Clinic. There were 11 males and 9 females with a mean age of 29 (range 18 to 41) years. Five were current smokers. In most instances the initial study was made in the autumn (ragweed) season. The subjects were requested to abstain from cigarettes and to discontinue allergy medicines on the day of the test.

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Care was taken to avoid performing the studies shortly after an upper respiratory tract infection (Picken, Niewoehner, and Chester, 1972).

At the initial evaluation the modified Medical Research Council respiratory symptoms questionnaire was completed (with questions relating to allergic history and previous medications). The chest was then auscultated and subjects with audible wheeze were excluded. Pulmonary function tests included spirometry using an electronic spirometer¹ and recording system previously described (Hankinson and Lapp, 1970). Flow volume curves of three forced vital capacity manoeuvres were recorded following two practice trials, the forced vital capacity (FVC), FEV₁, the forced expiratory flow at mid vital capacity (FEF₅₀), and the MMF being derived from the largest curve. The carbon monoxide transfer factor (TF) was obtained by the single breath method of Ogilvie *et al.* (1957), and alveolar volume (AV) by helium dilution during performance of the single breath test. Normal values for static lung volumes were those of Kory *et al.* (1961). Predicted values for TF were from Cotes (1968) in males and from Billiet, Baiser, and Naedts (1963) in females. The predicted FEF₅₀ in males was taken from the data of Lapp (1973), and for females from those of Cherniack and Raber (1972). Predicted values for MMF were from the work of Leuallen and Fowler (1955).

Closing volumes were measured using the resident nitrogen technique, expiratory flow rate being controlled by the subject to less than 0.5 l/s. At least three determinations were made in each subject and the average value was used. The CV and residual volume (RV) were added to obtain the closing capacity which was then expressed as a percentage of the total lung capacity (CC/TLC%). Normal values were those of Buist and Ross (1973a).

Transpulmonary pressure was obtained by subtraction of pressure at the mouth from oesophageal pressure measured by a 10 cm latex balloon connected by polyethylene tubing to a Satham transducer (PM131TC). The balloon was positioned in the lower third of the oesophagus with the tip approximately 42 cm from the nares. Flow was measured with a Fleisch No. 3 pneumotachograph and Satham PM 97 transducer, flow being integrated to obtain volume. Previous work in our laboratory has shown the results produced by this method to be comparable to those obtained when changes in volume are measured by body plethysmograph, as described by Woolcock *et al.* (1969).

A PDP 12 computer was used to calculate dynamic compliance in the following manner. Transpulmonary pressure, flow, and volume at the mouth were simultaneously digitized at 10 msec intervals with a 10 bit analog to digital converter. Zero flow points were identified at the end of inspiration and expiration by the computer which utilized the corresponding change in volume and transpulmonary pressure to calculate the dynamic compliance for each breath. The computer measurements were verified by hand measurement of the analog tracings of transpulmonary pressure, flow, and volume with good agreement between the two methods. Dynamic compliance was determined at 20, 40, and 60 breaths per minute, a minimum of 20 breaths being used at each frequency. Tidal volume was observed by the subject on an oscilloscope, and attempts were made to keep the volume constant and close to FRC. Further details of the apparatus and of our experience with Cdyn in normal subjects are available in previous publications from this laboratory (Seaton, Lapp, and Morgan, 1972; Morgan, Lapp, and Morgan, 1974). Use of the PDP 12 computer allowed final results for dynamic compliance at each breathing frequency to be available immediately at the end of the procedure. Cdyn was regarded as frequency dependent if the value at 60 breaths per minute was 80% or less of the value at 20 breaths per minute and when there was a statistically significant difference between the two ($p < 0.05$). If compliance was frequency dependent, the measurement was repeated after inhalation of isoprenaline. Tests were repeated in the winter in 18 patients, two having left the area. By this time, symptoms had resolved in all but two cases. Dynamic compliance measurements were repeated only in those subjects showing frequency dependence of compliance at the first study.

RESULTS

The results of conventional pulmonary function studies are seen in Table I.

Measurements of FVC, FEV₁, FEF₅₀, MMF, AV, and TF were within predicted normal limits. Statistical analysis of these conventional pulmonary function data using the paired *t* test showed no significant difference between the results obtained when the patients had symptoms of hay fever and those measured during the winter.

Closing capacities (CC/TLC%) were abnormal in only two of the subjects with symptoms; repeat measurement in the winter showed the closing capacities to have fallen to within predicted

¹Ohio Medical Products, Madison, Wis., USA—Model No. 800

TABLE I
LUNG VOLUMES, VENTILATORY CAPACITY, TRANSFER FACTOR, AND CLOSING CAPACITIES IN 20 SUBJECTS WITH HAY FEVER: MEAN, STANDARD DEVIATION, AND PERCENT PREDICTED

	VC (litres)	FEV ₁ (litres)	FEV %	FEF ₅₀ (l/sec)	MMF (l/sec)	RV (litres)	TF (ml min ⁻¹ torr ⁻¹)	CC/TLC %
With symptoms of hay fever	4.74 (0.98) 108.7%	3.88 (0.76) 106%	82.25 (7.33)	5.10 (1.09) 100.95%	4.16 (1.08) 100.61%	1.36 (0.36)	31.63 (7.74) 101.95%	32.38 ^a (5.3)
Without symptoms of hay fever ¹	4.64 (0.95)	3.73 (0.70)	81.3 (9.02)	5.01 (1.27)	4.04 (1.20)	1.45 (0.35)	32.56 (8.21)	32.51 ^a (4.4)

^a18 Subjects.^a16 Values.^a15 Values.

normal limits in both instances. Frequency dependence of Cdyn was demonstrated by one of these symptomatic subjects, compliance measured during the winter being normal. A further subject showed an abnormal slope of phase III (Buist and Ross, 1973b) and no identifiable closing volume when he had symptoms, but a normal slope of phase III and closing volume in the winter; this subject did not have frequency dependence of Cdyn. Closing volumes could not be detected at either study in three female subjects, the slope of phase III and the Cdyn being normal. No significant difference in closing capacity between the two studies could be detected by use of the paired *t* test.

The results of dynamic compliance are displayed in graphic form¹ (Fig. 1), Cdyn at 40 and 60 breaths per minute being expressed as a percentage of Cdyn at 20 breaths per minute. A summary of the results with the age and smoking

¹Full data in tabulated form are available from the authors on request

habits of individual subjects is given in Table II. Eight of 20 symptomatic subjects demonstrated a 15% or greater fall in compliance measured at 60 breaths per minute when compared with the values obtained at 20 breaths per minute (Fig. 1). After inhalation of isoprenaline this trend was reversed, Cdyn at 60 breaths per minute being equal to or greater than Cdyn at 20 breaths per minute in each instance (Fig. 2). Repeat evaluation in the winter of those demonstrating frequency dependence of Cdyn when they had hay fever revealed two subjects only in whom increase in breathing rate to 60 breaths per minute resulted in a significant fall in Cdyn (Fig. 3). Symptoms in these two subjects had not resolved with the end of the pollen season, both continuing to be troubled with rhinitis. Skin testing revealed sensitivity to multiple inhalants including house dust. Administration of isoprenaline produced no improvement on this occasion, Cdyn remaining frequency dependent (Fig. 4).

TABLE II
DYNAMIC COMPLIANCE ACCORDING TO SMOKING STATUS.

Subject	Age	Sex	Smoking Status ¹	Frequency Dependence of Dynamic Compliance			
				With Symptoms		Without Symptoms	
				Before Isoprenaline	After Isoprenaline	Before Isoprenaline	After Isoprenaline
SA	36	M	S	—			
EB	20	M	NS	—			
GB	21	F	S	—			
JB	26	F	NS	+			
EC	38	M	NS	+	—	+	+
JC	19	F	NS	—			
PD	41	M	NS	+	—	—	
AF	24	M	NS	+	—	—	
NG	38	F	NS	—			
JG	26	M	NS	—			
IG	25	F	S	—			
RH	31	F	NS	—			
JJ	28	M	P	+	—	—	
GL	18	M	S	+	—	—	
EM	36	M	NS	+	—	—	
SO	26	M	NS	—			
ES	32	F	NS	+	—	+	
LT	27	F	NS	—			
JT	27	F	NS	—			
JW	38	M	NS	—			

¹S = cigarette smoker; P = pipe smoker; NS = non-smoker.

FIG. 1. Dynamic compliance (C_{dyn}) at 40 and 60 breaths per minute as a percentage of C_{dyn} at 20 breaths per minute in 20 patients with symptoms of hay fever.

FIG. 2. Repeat measurement of C_{dyn} following inhalation of isoprenaline in the 8 patients who demonstrated frequency dependence of C_{dyn} .

DISCUSSION

Disease of the peripheral airways is presumed to be present if, when airway resistance and lung recoil pressure are normal, an increase in respiratory frequency is accompanied by a fall in dy-

FIG. 3. Dynamic compliance (C_{dyn}) measured in the winter in the 8 subjects who had demonstrated frequency dependence of C_{dyn} with hay fever.

FIG. 4. Repeat measurement of C_{dyn} following inhalation of isoprenaline in the 2 subjects who demonstrated frequency dependence of C_{dyn} in the winter.

amic compliance (Woolcock *et al.*, 1969). Frequency dependence of compliance has been demonstrated in the symptom-free asthmatic (Woolcock *et al.*, 1969; Levine *et al.*, 1970; Hill *et al.*, 1972), in patients with mild chronic bronchitis (Ingram and Schilder, 1967; Woolcock *et al.*, 1969; Levine *et al.*, 1970; McFadden and Linden, 1972; Gelb and Zamel, 1973), in normal subjects during upper respiratory tract infections (Picken *et al.*, 1972), in coal miners (Seaton *et al.*, 1972), and in otherwise healthy cigarette smokers (Ingram and O'Cain, 1971). In many instances support for the diagnosis of small airways disease has been forthcoming from the finding of abnormalities of gas exchange, disturbed $\dot{V}/\dot{Q}$ relationships on radioactive scanning, reduced maximal

expiratory flows at low lung volumes, and elevated closing volumes.

Separate measurements of airway resistance and elastic recoil were not made in our study. Abnormality of airway resistance is, however, unlikely with normal flow-volume curves and in the absence of lung hyperinflation. Reduction in elastic recoil due to emphysema is similarly unlikely in the presence of a normal gas transfer factor, a measurement which is sensitive to loss of pulmonary parenchyma. We feel, therefore, that the finding of frequency dependence of compliance has the same implications in our subjects as in previous studies where airway resistance and elastic recoil were measured separately and found to be normal.

In the present investigation care was taken to avoid inclusion of asthmatics, asthma being defined according to the criteria suggested by the American Thoracic Society (1962). Of 32 subjects who originally volunteered, 12 were rejected because of past history of attacks of wheezing or shortness of breath, or because of the discovery of expiratory wheeze on clinical examination, or reduced FEV₁ on spirometry. Of the subjects with symptoms of hay fever who were finally studied, 40% demonstrated frequency dependence of compliance which disappeared after inhalation of isoprenaline and when the symptoms remitted at the end of the pollen season. The two subjects who exhibited frequency dependent behaviour in the winter had retained their symptoms and did not improve on this occasion with inhalation of bronchodilators. Hill *et al.* (1972), in their study of symptom-free asthmatics, found two subjects in whom compliance did not improve with bronchodilators. They suggested that these patients might have more severe small airways obstruction than those who improved with bronchodilators, perhaps the result of mucus plugging and mucosal oedema rather than muscular spasm. It is also possible that the bronchial reaction in these subjects was mediated by a type III immunological response which would be expected to result in a more severe reaction resistant to the effects of isoprenaline (Pepys, 1973).

In the present study two subjects who were smokers showed frequency dependence of compliance when they had hay fever and normal dynamic compliance during the winter (Table II). No attempt was made to change their smoking habits over the period of study. Abnormalities of dynamic compliance in asymptomatic smokers have previously been described by Ingram and O'Cain (1971). In our subjects, however, it is un-

likely that the abnormal compliance can be attributed solely to the effects of smoking as the frequency dependent behaviour was seen only in association with hay fever symptoms.

Reduction in maximal expiratory flow rates at low lung volumes has been demonstrated in symptom-free asthmatics but was found to correlate poorly with the presence of frequency dependence of compliance (Hill *et al.*, 1972). Asthmatics with normal flow rates at low lung volumes did demonstrate frequency dependence of compliance. In a study of airways function in mild respiratory illness, Fridy *et al.* (1974) showed that no difference could be detected between expiratory flow rates measured during the illness and those obtained following recovery except when they were measured after inhalation of a helium-oxygen mixture. Even then a significant reduction of flow rates during the illness was seen only in smokers. In our patients with hay fever, flow rates were within normal limits and not different from those obtained when symptoms had resolved in the winter. These normal flow rates at low lung volumes may reflect solely the wide range of 'normality' for the measurement. It is possible, however, that the extent of peripheral airways involvement in hay fever and mild viral respiratory infections is sufficient to result in frequency dependence of compliance but not to cause significant reduction in overall flow rates.

Abnormal 'closing volumes' have been reported in 84% of a group of symptom-free asthmatics (McCarthy and Milic-Emili, 1973). In two of our subjects with hay fever the closing capacity was abnormal but reverted to normal during the winter. One of these was a current smoker and also demonstrated frequency dependence of compliance when he had symptoms. No significant difference could be detected between closing capacities measured at the time of maximal symptoms and those obtained during remission. In the study of Fridy *et al.* (1974), closing volumes were abnormal during the respiratory illness in smokers only, and became normal when repeated following recovery from the infection. The other three smokers in our study for whom repeat measurements were available had normal closing capacities during their hay fever and these did not change significantly when repeated in the winter.

It seems likely that, in a significant proportion of subjects with hay fever, the pathological changes are not restricted to the nose but also involve the airways. This has been suggested by the frequent occurrence of attacks of wheezing in subjects with hay fever at times of heavy pollen

exposure, and by the uncovering of abnormal bronchial reactivity following the administration of acetylcholine (Vondra *et al.*, 1971; Ionescu, 1973; Grossman and Putnam, 1975). In our study, reversible abnormality of airway function has been demonstrated in subjects with hay fever who exhibit normal pulmonary function by conventional testing. Intrinsic narrowing or obstruction of peripheral airways seems the most likely cause for these results although changes in elastic recoil and resistance have not been totally excluded. The measurement of dynamic compliance at different breathing frequencies appears a sensitive test for the detection of these abnormalities.

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REFERENCES

- American Thoracic Society (1962). Diagnostic standards for nontuberculous respiratory diseases. *American Review of Respiratory Diseases*, **85**, 762.
- Billiet, L., Baiser, W., and Naedts, J. P. (1963). Effet de la taille, du sexe et de l'âge sur la capacité de diffusion pulmonaire de l'adulte normal. *Journal de Physiologie*, **55**, 199.
- Buist, A. S. and Ross, B. B. (1973a). Predicted values for closing volumes using a modified single breath nitrogen test. *American Review of Respiratory Diseases*, **107**, 744.
- and — (1973b). Quantitative analysis of the alveolar plateau in the diagnosis of early airway obstruction. *American Review of Respiratory Diseases*, **108**, 1078.
- Cherniack, R. M. and Raber, M. B. (1972). Normal standards for ventilatory function using an automated wedge spirometer. *American Review of Respiratory Diseases*, **106**, 38.
- Cotes, J. E. (1968). *Lung Function*, 2nd edition, p. 375. F. A. Davis, Philadelphia. Blackwell, Oxford.
- Fridy, W. W., Jr., Ingram, R. H., Jr., Hierholzer, J. C., and Coleman, M. T. (1974). Airways function during mild viral respiratory illnesses. *Annals of Internal Medicine*, **80**, 150.
- Gelb, A. F. and Zamel, N. (1973). Simplified diagnosis of small-airway obstruction. *New England Journal of Medicine*, **288**, 395.
- Grossman, J. and Putnam, J. S. (1975). Small airway obstruction in allergic rhinitis. *Journal of Allergy and Clinical Immunology*, **55**, 49.
- Hankinson, J. L. and Lapp, N. L. (1970). Time-pulse generator for flow-volume curves. *Journal of Applied Physiology*, **29**, 109.
- Hill, D. J., Landau, L. I., and Phelan, P. D. (1972). Small airway disease in asymptomatic asthmatic adolescents. *American Review of Respiratory Diseases*, **106**, 873.
- Ingram, R. H., Jr. and O'Cain, C. F. (1971). Frequency dependence of compliance in apparently healthy smokers versus non-smokers. *Bulletin de Physio-Pathologie Respiratoire*, **7**, 195.
- and Schilder, D. P. (1967). Association of a decrease in dynamic compliance with a change in gas distribution. *Journal of Applied Physiology*, **23**, 911.
- Ionescu, R. (1973). Allergic rhino-sinusitis and the allergy of inferior respiratory pathways (Rumanian). *Oto-rino-laringologig*, **18**, 37.
- Kory, R. C., Callahan, R., Boren, H. G., and Syner, J. C. (1961). The Veterans Administration-Army cooperative study of pulmonary function. I. Clinical spirometry in normal men. *American Journal of Medicine*, **30**, 243.
- Lapp, N. L. (1973). Physiological approaches to detection of small airway disease. *Environmental Research*, **6**, 253.
- Leuallan, E. C. and Fowler, W. S. (1955). Maximal midexpiratory flow. *American Review of Tuberculosis*, **2**, 783.
- Levine, G., Housley, E., Macleod, P., and Macklem, P. T. (1970). Gas exchange abnormalities in mild bronchitis and asymptomatic asthma. *New England Journal of Medicine*, **282**, 1277.
- McCarthy, D. and Milic-Emili, J. (1973). Closing volume in asymptomatic asthma. *American Review of Respiratory Diseases*, **107**, 559.
- McFadden, E. R., Jr. and Linden, D. A. (1972). A reduction in maximum mid-expiratory flow rate; a spiographic manifestation of small airway disease. *American Journal of Medicine*, **52**, 725.
- Macklem, P. T. (1972). Obstruction in small airways—a challenge to medicine. *American Journal of Medicine*, **52**, 721.
- May, K. L. and Kotowska, A. (1965). Rhinitis and asthma—spiographic examination of rhinitic patients. *Allergie und Asthma*, **11**, 275.
- Morgan, W. K. C., Lapp, N. L., and Morgan, E. J. (1974). The early detection of occupational lung disease. *British Journal of Diseases of the Chest*, **68**, 75.
- Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W. (1957). A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *Journal of Clinical Investigation*, **36**, 1.
- Pepys, J. (1973). Conference summary. *Chest*, **63**, 72S.

- Picken, J. J., Niewoehner, D. E., and Chester, E. H. (1972). Prolonged effects of viral infections of the upper respiratory tract upon small airways. *American Journal of Medicine*, **52**, 738.
- Seaton, A., Lapp, N. L., and Morgan, W. K. C. (1972). Lung mechanics and frequency dependence of compliance in coal miners. *Journal of Clinical Investigation*, **51**, 1203.
- Vondra, V., Zelený, M., Ráthová, E., Horák, J., and Vondrová, V. (1971). Acetylcholine-adrenalin test and the latent bronchopulmonary spastic syndrome in cases with allergic vasomotor rhinitis. *Vnitřní Lékařství*, **17**, 673.
- 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.

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