Inspiratory Obstruction

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Summary: Obstructing lesions of the trachea and larynx which cause a predominantly inspiratory obstruction can be satisfactorily diagnosed by measuring both $F.I.V._{\cdot 1}$ and $F.E.V._{\cdot 1}$. Chronic airways obstruction involving intrathoracic airways produces a much lower $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage than normal, whereas obstruction to larynx and trachea causes a raised $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage. If flow-volume measurements are not available the $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage should provide a simple and useful method for diagnosis of upper airways obstruction.

In one of the patients reported a predominantly inspiratory obstruction caused CO_2 retention. In patients with airways obstruction the correlation between P_{CO_2} and $F.I.V._{\cdot 1}$ was found to be the same as between P_{CO_2} and $F.E.V._{\cdot 1}$. This suggests that respiratory failure can be caused by either inspiratory or expiratory airways obstruction and that neither is of greater importance in producing CO_2 retention.

Introduction

Airflow obstruction is commonly assessed by analysis of a forced expiration from total lung capacity. Such an analysis is usually made in terms of forced expired volume in one second ($F.E.V._{\cdot 1}$) or the ratio of $F.E.V._{\cdot 1}$ to vital capacity (V.C.). These measurements and others, such as the peak expiratory flow rate (P.E.F.R.), are used to detect airways obstruction and monitor its response to treatment. Dynamic compression of large central airways during expiration, however, led Macklem *et al.* (1965) to question the value of tests using a forced expiration to monitor changes in calibre of small peripheral airways, and Saunders (1967) found the peak inspiratory flow rate useful in assessing the response to bronchodilators in patients with emphysema. Tests made during inspiration may therefore be of value in assessing obstruction to airflow.

Obstruction to airflow is usually considered in terms of airways within the chest, and extrathoracic airways obstruction is consequently rarely identified unless clinically obvious. The importance of extrathoracic airways obstruction has been realized comparatively recently by paediatricians, who now recognize that large adenoids and tonsils may produce respiratory failure which presents with fluid retention and evidence of pulmonary hypertension (Bland *et al.*, 1969). Miller and Hyatt (1969) have also drawn attention to the diagnosis of obstructing lesions of larynx and trachea in adults. Their elegant analysis, however, includes flow-volume loops, which are not always available and are not easy to interpret when they are to hand. This paper attempts to assess a simple method whereby the ratio of forced expired volume in one second ($F.E.V._{\cdot 1}$) to forced inspired volume in one second ($F.I.V._{\cdot 1}$) is used as a means of discriminating between intrathoracic and extrathoracic airways obstruction and assessing obstruction to airflow.

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Methods and Subjects

Patients performed a standard forced expiratory manoeuvre to obtain the $F.E.V._{\cdot 1}$ and forced vital capacity (F.E.V.C.), using a lightweight low-resistance spirometer with the CO_2 absorber removed. The inspiratory test followed a short period of tidal breathing at rest when the patient was told to expel all the air from his resting end expiratory level. This expulsion of expiratory reserve volume was unhurried, but once residual volume was achieved the patient was asked to inspire as hard and as fast as possible until total lung capacity was reached. This technique was acquired rapidly by patients, who found it slightly more difficult to perform than a forced expiration; this had also been observed by McNeill *et al.* (1959). From the spirogram the $F.I.V._{\cdot 1}$ and inspiratory V.C. (F.I.V.C.) were obtained.

A Wright peak flow meter was used to measure peak expiratory flow rate, and with the adaptation of Nairn and McNeill (1963) the peak inspiratory flow rate (P.I.F.R.) was also measured.

A two-stage rebreathing method was used to measure the oxygenated mixed venous P_{CO_2} (Campbell and Howell, 1962).

Five healthy subjects (three men and two women, mean age 28 years) acted as normals.

Fifteen patients with chronic airways obstruction were studied. All had an $F.E.V._{\cdot 1}$ of less than 1·5 litres (mean 0·91 l., S.E. of mean 0·08 l.) and a percentage of $F.E.V._{\cdot 1}/F.E.V.C.$ of less than 60 (mean 37·1, S.E. of mean 2·1).

Seven patients had chronic obstructive bronchitis and four had emphysema as well as chronic bronchitis. Four patients had asthma, and two of these had persistent cough and sputum production. All were in hospital having recovered from a recent increase in airways obstruction.

Results

The results are summarized in Fig. 1, which shows the percentage of $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ to be much lower than normal in patients with chronic airways obstruction. The mean value of $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ for patients was 43·0% compared with 86·4% in normals, and this difference is a highly significant one. The percentage F.E.V.C./F.I.V.C. can be seen to be similar in both groups, and this index is therefore of no help in discriminating between normals and patients with airways obstruction. The percentage P.E.F.R./P.I.F.R. showed a lower value in patients with airways obstruction, and the mean value of 83·7% is similar to that found by Saunders (1967) in his patients with emphysema. The low $F.E.V._{\cdot 1}/F.E.V.C.$ percentage is to be expected in patients with airways obstruction, but the $F.I.V._{\cdot 1}/F.I.V.C.$ shows only a minor reduction.

In summary, a low $F.E.V._{\cdot 1}$ in combination with low $F.E.V._{\cdot 1}/F.E.V.C.$ and $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentages represents the picture of intrathoracic airways obstruction. Fig. 1 also shows the values obtained in four patients with obstructing lesions of trachea and larynx, and a striking difference is seen in terms of $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage, which is less obvious when judged by P.E.F.R./P.I.F.R. percentage. It would therefore appear that the $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage provides

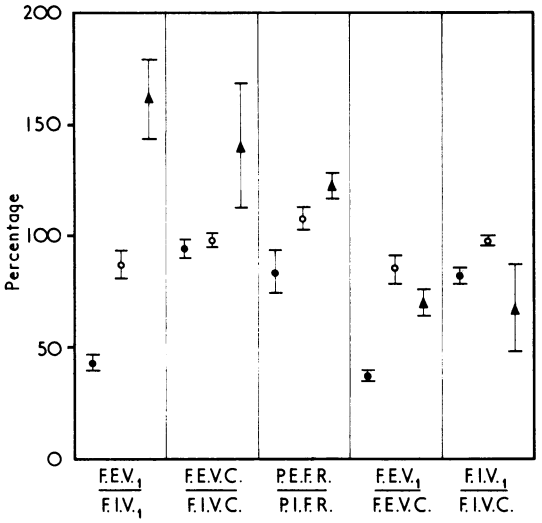

FIG. 1.—Various ratios (expressed as a percentage) of expiratory to inspiratory ventilatory capacity. Mean and S.E. of mean. O Normal. ● Patients with chronic airways obstruction. ▲ Patients with lesions of trachea and larynx.

the most satisfactory discrimination between intrathoracic airways obstruction and obstructing lesions of trachea and larynx.

Details concerning the four patients with predominantly inspiratory obstruction are given in the Table.

Discussion

Detection of Laryngeal and Tracheal Obstruction

Miller and Hyatt (1969) studied patients with upper airways obstruction and also studied the effect of adding obstruction to airflow in normals. They found flow-volume loops useful in enabling them to classify the lesions involving major airways. They proposed that a fixed stenosis will cause abnormal flow rates in both inspiratory and expiratory phases. If the obstruction is variable, in that airway size is altered by transmural pressure gradients, the location of the lesion becomes important. Intrathoracic airways obstruction will cause a predominantly expiratory flow limitation whereas obstruction to upper airways will cause inspiratory obstruction.

This classification has been vindicated by analysis of the $F.E.V._{\cdot 1}$ and $F.I.V._{\cdot 1}$ in the four patients reported in this paper. In two (Cases 1 and 2) the lesion was laryngeal and variable, with a much lower $F.I.V._{\cdot 1}$ than $F.E.V._{\cdot 1}$, which was only slightly lower than predicted. In Cases 3 and 4 the lesion was relatively fixed, causing both $F.E.V._{\cdot 1}$ and $F.I.V._{\cdot 1}$ to be reduced greatly. Both these latter patients had tracheal stenosis and showed a raised $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage, indicating that the obstruction was largely in the upper airways.

A major objection to tests of inspiratory flow limitation lies in the fact that these tests are more effort-dependent than tests involving a forced expiration. This has not proved to be a significant problem in the present study, and it is noteworthy that in all patients with chronic airways obstruction the $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ was less than 100% and the standard deviation about the mean value of 43·0% was 12·3% despite a heterogeneous group of patients with varying degrees of airways obstruction. McNeill *et al.* (1959) found the coefficient of variation to be similar in forced expiratory and forced inspiratory spirograms, and this has been confirmed by Tandon and Campbell (1970). The P.E.F.R./P.I.F.R. index was less satisfactory, but though it exceeded 100% in most healthy subjects this occurred in only 2 of the 15 patients. McNeill *et al.* (1959) also reported the P.E.F.R./P.I.F.R. to be between 114 and 136% in normals and more variable than forced spirometry. Saunders (1967) had found P.I.F.R. to be a satisfactory measurement and observed the within-patient variance of P.I.F.R. not to be excessive, and of the same order of magnitude as P.E.F.R.

It is reasonable to conclude that with proper attention to detail the $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ index is not seriously affected by a variability of effort and is a satisfactory measurement to make. From the viewpoint of diagnosis of obstructing lesions of trachea and larynx, a low $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage makes such a diagnosis unlikely and would indicate predominantly intrathoracic airways obstruction. A percentage $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ in excess of 100% makes a diagnosis of upper airway stenosis most likely, and this will require endoscopy or tomography for confirmation. Flow-volume measurements will provide useful additional information, and their analysis is helped by measuring the maximum flow attained at a lung volume in the middle of the vital capacity (Jordanoglou and Pride, 1968).

Details of Patients with Obstructing Lesions of Trachea or Larynx

Case No.	Sex	Age	Diagnosis	F.E.V.$_{\cdot 1}$ (Litres)	F.E.V.C. (Litres)	F.I.V.$_{\cdot 1}$ (Litres)	P_{VCO_2} (mm. Hg.)
1	M.	63	?Cancer of larynx	2·7	4·1	1·3	64
2	M.	48	Cancer of larynx	2·1	3·3	1·6	40
3	F.	64	Cancer of bronchus	0·4	0·5	0·3	43
4	F.	55	Goitre	0·8	1·2	0·5	58

CO_2 Retention

One patient (Case 1) presented with a raised mixed venous P_{CO_2} and only a minor reduction in $F.E.V._{\cdot 1}$. In the absence of inspiratory obstruction this would suggest primary alveolar hypoventilation with an insensitive respiratory centre. Finding a low $F.I.V._{\cdot 1}$, and hence a high $F.E.V._{\cdot 1}/F.I.V._{\cdot 1}$ percentage, raised the possibility that inspiratory flow limitation may be more important than expiratory obstruction in causing CO_2 retention. Milic-Emili and Tyler (1963) found evidence to suggest that the CO_2 stimulus to the respiratory motor neurones was related to inspiratory work and bore no constant relation to expiratory activity. It could therefore be envisaged that respiratory motor neurone activity would be particularly sensitive to inspiratory obstruction, which would markedly alter inspiratory work.

This possibility is of interest because of the poor correlation observed between P_{CO_2} and $F.E.V._{\cdot 1}$ (Clark, 1968). To examine this point I have related the P_{CO_2} to both $F.E.V._{\cdot 1}$ and $F.I.V._{\cdot 1}$, the results being shown in Fig. 2. As can be seen, the correlation is no better when $F.I.V._{\cdot 1}$ is substituted for $F.E.V._{\cdot 1}$. I have also studied a patient with primary alveolar hypoventilation ($F.E.V._{\cdot 1}$=2·6 l., P_{VCO_2}=58 mm. Hg.) and found a higher $F.I.V._{\cdot 1}$ ($F.I.V._{\cdot 1}$=3·5 l.) supporting the diagnosis of

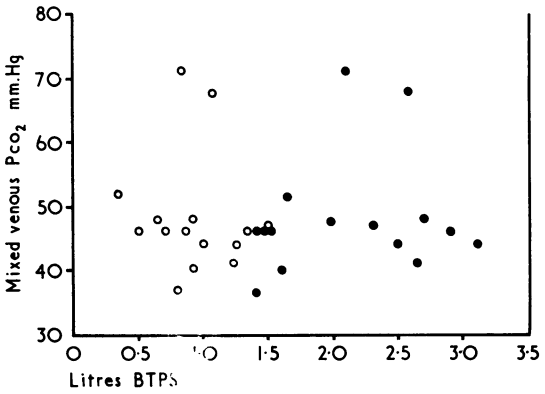

FIG. 2.—$F.E.V._{\cdot 1}$ (O) and $F.I.V._{\cdot 1}$ (●) related to resting mixed venous P_{CO_2} in patients with chronic airways obstruction.

minor intrathoracic airways obstruction with predominantly expiratory flow limitation.

It therefore seems unlikely that inspiratory flow limitation is more prone to cause CO_2 retention than expiratory obstruction. This suggests that CO_2 retention is caused by obstruction to airflow and is independent of the phase of breathing that is predominantly affected.

I would like to thank Miss Judith Turner for help, and my colleagues for allowing me to study patients under their care.

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Cancer of the Bladder in Patients treated with Chlornaphazine

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Summary: Two patients treated for Hodgkin's disease with chlornaphazine developed cancer of the bladder five and six years after treatment with the drug had been stopped.

Introduction

The carcinogenic effect of 2-naphthylamine metabolites on the urinary bladder is well documented (Bonser *et al.*, 1952; Scott and Boyd, 1953; Boyland and Manson, 1955).

Chlornaphazine, a derivative of 2-naphthylamine, has previously been used in the treatment of polycythaemia and Hodgkin's disease. Increased incidence of bladder cancer was observed in patients with polycythaemia treated with chlornaphazine as compared with patients who did not receive such treatment (Thiede *et al.*, 1964). Similarly, cancer of the urinary bladder developed in some cases of Hodgkin's disease during treatment with chlornaphazine (Videbæk, 1964). Because of this the drug was withdrawn, at least in Denmark.

The present communication describes two cases of cancer of the urinary bladder occurring five and six years after chlornaphazine treatment was stopped.

Case 1

The patient was a woman aged 40. In 1957 Hodgkin's disease was diagnosed by biopsy from enlarged cervical glands, afterwards treated with *x*-ray irradiation. From 1959 to 1965 the pelvic lymph nodes became enlarged on four occasions, treated each time with *x*-ray irradiation (total dose 5,590 r). In 1968 lymphangiography showed enlargement of the para-aortic glands and Mobaltron treatment was given. After this there were no signs of activity of Hodgkin's disease.

Anti-neoplastic drugs were given as follows: chlornaphazine in daily doses of 200 mg. to a total of about 85 g. from October 1962 to November 1963; cyclophosphamide (Endoxana) 50-100 mg. daily from January 1964 to November 1965; and procarbazine chloride (Natulan) 150-100 mg. daily from May to August 1968. From March 1968 to January 1969 prednisone was added in doses of 5-45 mg. daily.

Bladder Symptoms.—In November 1965, during treatment with cyclophosphamide, the first episode of macroscopic haematuria, severe dysuria, urgency, and frequency occurred. Cystoscopy showed a "chemical cystitis" with mucosal telangiectasias and fibrin deposits, but no proliferative changes. These were interpreted as a cyclophosphamide cystitis, so the drug was discontinued.

In November 1966, June 1968, and November 1968 episodes of gross haematuria occurred with severe pain on micturition. Cystoscopy was performed each time, on the first two occasions showing only slight oedema, fibrin deposits, and mucosal hypertrophy. In November-December 1968 a tumour was seen on the posterior wall of the bladder above the orifice of the right ureter. Urinary sediment contained abnormal cells indicating tumour growth, and biopsy showed a papillomatous bladder carcinoma, grade I, which was treated with electrocoagulation. In January 1969 the patient died of bronchopneumonia with septicaemia after several severe haemorrhages from the bladder resistant to irrigational and other therapy.

Necropsy.—Macroscopic tumour was not found in the urinary bladder. In the right pelvis and upper part of the right ureter several flat mucosal haemorrhages 5-10 mm. in diameter were seen. The mucosa of the trigonum and posterior wall of the bladder was granulated and covered with yellow incrustations and fibrin deposits. Histology showed no changes. In the pre-aortic glands and spleen changes typical of Hodgkin's disease were seen. No changes were found in the thoracic glands. Bronchopneumonia was found in the right lung.

Laboratory Tests.—The most important were blood platelet counts from 10,000 to 40,000/cu. mm.; coagulation tests (recalcification time, Quick time, thrombin time, partial thromboplastin time, factor X, factor V, prothrombin (factor II + factor VII)), no significant changes; serum creatinine 1 mg./100 ml.

Case 2

This patient was a 68-year-old woman. In 1927 enlargement of the cervical glands of unknown aetiology was treated with local injections, ultraviolet light, and *x*-ray irradiation. In 1943 hysterectomy was performed because of profuse and irregular uterine bleedings.

Hodgkin's disease was diagnosed in 1959 by biopsy from an enlarged left supraclavicular lymph node. From November 1962 to May 1967 the disease gradually spread to the right supraclavicular, right axillary, and left axillary nodes, showing varying degrees of nodular enlargement. In May 1967 hilar enlargement was found, and from December 1967 there was infiltration in both lung apices with accompanying cough and exertional dyspnoea. In December 1968 a cavity developed in the left apex. Neither tumour cells nor tubercle bacilli were found. In September 1969 another infiltration occurred near the left pulmonary hilus.

Radiation therapy was given in two series: in September 1967 Mobaltron on the neck, axillae, supraclavicular regions, and the mediastinum (total dose 400 r); in November 1969 conventional *x*-ray irradiation on the central infiltration (total dose 5,200 r).

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