Pulmonary function in acromegaly

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Evans, C. C., Hipkin, L. J., and Murray, G. M. (1977). Thorax, 32, 322–327. Pulmonary function in acromegaly. The lung volumes of 12 female and eight male patients with acromegaly, chosen because of the absence of associated cardiorespiratory disease, were determined physiologically and radiographically. Enlarged lung volumes were found in half the males but in none of the females, due allowance being made for the presence of a significant thoracic kyphosis. Upper airway narrowing was suggested by an increase in the expiratory–inspiratory flow rate ratio in six patients, four of whom were male, and acromegaly of the larynx was confirmed in the three subjects who consented to laryngoscopy. Upper airway obstruction is more likely to account for respiratory death in acromegaly than disordered pulmonary function in enlarged acromegalic lungs. Neither of these respiratory findings could be correlated with the fasting level of growth hormone but there was a suggestion that they were more likely to occur when the duration of the disorder was longer.

Enlargement of visceral organs such as the heart and kidney is a well recognised manifestation of acromegaly (Cushing and Davidoff, 1927; Gordon et al., 1962). The lung volumes in this condition have been measured in few subjects and the results are disparate. Brody et al. (1970) showed that in six male acromegals the total lung capacity (TLC), functional residual capacity (FRC), and vital capacity (VC) were increased up to a mean of 140% predicted, whereas in four females these volumes were normal. In contrast, Toppell et al. (1973) found that the TLC and VC were increased in seven females with acromegaly up to a mean of 111% and 116% predicted respectively. They confirmed increases in the TLC, VC, and residual volume (RV) in nine males with the disorder, up to 122% predicted.

The mechanism by which lung growth occurs in acromegaly is not clear. Brody et al. (1970) deduced that alveolar size but not number is increased by growth hormone (HGH) excess and they subsequently showed a reduction in lung volumes and alveolar size in hypopituitarism (Jain et al., 1973). Lung morphological data are not available in man with acromegaly, which is surprising since Wright et al. (1970) reported that acromegals die prematurely and that death attributable to respiratory disease occurs at a frequency three times greater than expected in both sexes. There is no adequate explanation for this finding to date. The only clue to respiratory risks comes from Kitahata (1971) who described upper airway narrowing complicating anaesthesia in three patients with acromegaly.

The present study was undertaken to explore some of these problems.

Material and methods

Twenty-four patients (8 males and 16 females) attending endocrine clinics gave verbal informed consent to the procedures. Fasting HGH levels were estimated by a solid phase radioimmunassay system (Abbott Laboratories). Results are expressed in terms of the Abbott standard, 1 μg of which is equivalent to 1.25 IU of WHO standard 66/217. Acromegaly was considered active when HGH suppression did not occur during an oral glucose tolerance test.

A detailed personal, occupational, and medical history was recorded followed by a full clinical examination. Spirometry was performed with a low resistance spirometer (Bernstein et al., 1952) with the patient seated and the FRC was measured using a closed-circuit helium dilution technique. The diffusing capacity for carbon monoxide (TLCO) was measured by the single-breath method of Ogilvie et al. (1957). Krogh’s permeability factor
or transfer coefficient ($K_{CO}$) was derived by dividing $Tl_{CO}$ by the alveolar volume which was calculated by adding the inspired volume during the single-breath procedure to the RV obtained by the closed-circuit helium dilution.

The predicted values for lung volumes, spirometry, and gas transfer were taken from Cotes (1968). For $K_{CO}$ the predicted values were those of Van Ganse et al. (1972).

Standard six-foot postero-anterior and left lateral chest radiographs were taken in deep inspiration. These were read independently and the angle of kyphosis was recorded (Bradford et al., 1974). The presence or absence of scalloping of the posterior surfaces of the vertebral bodies was noted (Murray and Jacobson, 1971) as well as emphysema (Simon, 1971). Determination of the radiographic TLC was a modification of that described by Barnhard et al. (1960) by Loyd et al. (1966).

A 12-lead electrocardiogram was recorded. The alpha 1 antitrypsin level was measured on a sample of venous blood by radioimmunassay (Boehringwerke, A G). A 10-item serum multiple analysis profile consisting of total protein, albumin, bilirubin, alkaline phosphatase, calcium, uric acid, glucose, lactic dehydrogenase, creatinine, and aspartate transaminase was performed.

Results

CLINICAL

None of the subjects was a pituitary giant. The mean age of men and women was similar but the duration of the disease crudely assessed by the patient and his relatives was longer in men than in women. Growth hormone estimations indicated active acromegaly in all but one—a female, KM—in spite of previous treatment in 11, five of whom were receiving either steroid or thyroxine replacement or both, according to pituitary function. Two were diabetics (MS and SA), and SA took pituitary snuff for diabetes insipidus. Thyroid cysts were found in four, and in one (KH) this was retrosternal. Eight patients were hypertensive, and in three (EW, KH, MS) there were associated electrocardiographic abnormalities. The ECG of MS also showed a right bundle-branch block pattern. Thirteen subjects smoked cigarettes, but only two (EW and KH) had symptoms of chronic bronchitis. DR suffered from bronchiectasis confirmed by bronchography. The results of EW, DR, KH, and MS have been excluded from the mean values because these associated disorders will affect pulmonary function. Thus results are available for 12 female and 8 male acromegals, in all of whom pulmonary function might reasonably be expected to be normal.

PULMONARY FUNCTION

Tables 1 and 2 show pulmonary function results. The TLC was increased in men (112% predicted) but not in women (101% predicted). This significant increase in men was due mainly to an increase in VC (120% predicted) but the RV was not significantly increased (109%). The VC was higher than predicted in women (109%). In both sexes the diffusing capacity and transfer coefficient were normal. The forced expired volume in one second ($FEV_1$) was within the normal range in all but two subjects (DD and KM) in whom the values were low and neither smoked cigarettes. These two subjects also showed the lowest values for maximum mid inspiratory flow rate (MIFR) and maximum mid expiratory flow rate (MEFR) for their sex. MEFR/MIFR ratios were uniformly reduced in those four subjects excluded from calculation of the overall means because of co-

### Table 1 Pulmonary function in eight males with acromegaly

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Duration of disease (yr)</th>
<th>Fasting growth hormone (µg/l)</th>
<th>Forced vital capacity %pred.</th>
<th>Forced expiratory volume %pred.</th>
<th>Residual volume %pred.</th>
<th>Total lung capacity %pred.</th>
<th>Transfer factor %pred.</th>
<th>Krogh's permeability constant ($K_{CO}$) %pred.</th>
<th>MEFR MIFR ratio</th>
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<td>119</td>
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<td>49.2</td>
<td>119.8</td>
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<tr>
<td>P obs. v pred.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;0.01</td>
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<td>&gt;0.05</td>
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existing pulmonary disease and were significantly increased above the normal for this laboratory (1.5) in two females and four males.

**RADILOGRAPHIC APPEARANCES**

These results are summarised in Table 3 which shows that radiological emphysema was found in only one patient and posterior vertebral scalloping in three males but no females. No retrosternal thyroid swellings were detected in any of these 20 subjects. A significant thoracic kyphosis was present in 10 (50%) of the subjects, there being four men and six women with an angle of kyphosis greater than anticipated for the patient's age (Murray, 1976 unpublished observations).

Table 3 lists the 10 subjects with a normal thoracic angle of kyphosis, and it will be seen that both the physiological and radiological assessment of TLC exceeds predicted values in males but not in females.

**BLOOD ANALYSES**

The alpha 1 antitripsin level was normal in every subject. Serum multiple analyses confirmed hyperglycaemia in the diabetics. The lactic dehydrogenase was found to be up to twice the normal value in 13 of the 24 subjects studied. The alkaline phosphatase was raised in TS, who had osteomyelitis of the femur. All other values were in the normal range.

**Discussion**

The increased lung volumes in male acromegals

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**Table 2** Pulmonary function in 16 females with acromegaly

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Duration of disease (yr)</th>
<th>Fasting growth hormone (mIU/l)</th>
<th>Forced vital capacity % pred.</th>
<th>Forced expiratory volume % pred.</th>
<th>Residual volume % pred.</th>
<th>Total lung capacity % pred.</th>
<th>Transfer factor % pred.</th>
<th>Krogh's permeability constant (Kco) % pred.</th>
<th>MEFR ratio</th>
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n=12

<table>
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<tr>
<th>Subject</th>
<th>Angle of kyphosis (degrees)</th>
<th>Posterior vertebral scalloping</th>
<th>Emphysema</th>
<th>Total lung capacity % pred.</th>
<th>X-ray</th>
<th>Helium</th>
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</table>

**Table 3** Results of chest radiographs in 20 subjects with acromegaly and comparison of radiographic with physiological total lung capacity in those subjects without a significant kyphosis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Angle of kyphosis (degrees)</th>
<th>Posterior vertebral scalloping</th>
<th>Emphysema</th>
<th>Total lung capacity % pred.</th>
<th>X-ray</th>
<th>Helium</th>
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</table>

**Discussion**

The increased lung volumes in male acromegals

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contrast with the normal values found in females with the disorder, and these findings confirm those of Brody et al. (1970). The angle of the thoracic kyphosis has not been considered either by these workers or by Toppel et al. (1973). A significant thoracic kyphosis occurred in half the subjects in our study and in 60% of 20 acromegals reported by Lang and Bessler in 1961. Predicted values for lung volumes vary according to age, sex, and height so that when a greater than normal angle of kyphosis is present the subject's overall height will be underestimated and hence the predicted lung volumes will be underestimated. Thus measured lung volumes will be greater than predicted. To overcome this difficulty Table 3 shows the physiological and radiological total lung capacities for the 10 subjects (4 males and 6 females) in whom the angle of kyphosis was in the normal range for age. Here, too, male acromegals have a larger than predicted TLC and contrast with females with normal volumes. Failure to consider the angle of kyphosis is the likely explanation for Toppel et al. (1973) finding large lungs in three of seven females with acromegaly although their results were weighted by one subject, who smoked, in whom there was evidence of lung overinflation and airways obstruction.

Several factors contribute to the thoracic kyphosis; the intervertebral discs are narrowed anteriorly and widened posteriorly, new bone apposition occurs along the anterior border of the thoracic spine, and lengthening of the ribs, especially at the costochondral junctions, produces a larger chest cavity which exaggerates the kyphosis (Steinbach et al., 1959).

In the absence of a plethysmograph to measure lung volume we estimated the total lung capacity radiographically and compared the results with those derived from helium dilution (Table 3). Radiographic measurement of TLC has been shown to correlate very well with plethysmographic determination (Loyd et al., 1966). Subjects with a significant kyphosis were ignored since the radiographic method also depends upon predictions of pulmonary blood volume and tissue volume derived from nomograms incorporating the subject's height. By this technique the lungs of female acromegals were of normal volume, but in males the radiographic value was even greater than the helium measurement, suggesting that in these men with large lungs there may have been some air trapping (Bedell et al., 1956).

The undoubted difference between the sexes in lung volumes in acromegaly confirmed in this study was first noted by Cushing and Davidoff in 1927. They showed that splanchnomegaly was less marked in females; moreover, the largest lungs at necropsy reported in their monograph were both male. Oestrogens have in fact been given to block the metabolic effects of growth hormone currently attributed to somatomedin (Schwartz et al., 1969; Wiedemann and Schwartz, 1972).

The normal values for TLC and KCO reported here suggest that lung growth is associated with an increase in alveolar size and not number. This is in keeping with current theories of postnatal lung growth which up to the age of eight years occurs by multiplication of alveoli and thereafter by an increase in the size of existing alveoli (Dunnill, 1962; Angus and Thurlbeck, 1972). In acromegaly the enlargement of other viscera, such as the heart and kidneys, results from an increase in cell size (Daughaday, 1968), and tissues like the renal glomerulus increase in size rather than number (Cushing and Davidoff, 1927). Bartlett in 1971 studied the effect of HGH on the rat lung but this experiment produced a disease more similar to human gigantism than acromegaly because the epiphyses of rat long bones never close (Astwood, 1955). The effect, therefore, of HGH on human lung is not fully understood and requires further investigation.

Our results have not apparently supported in life the retrospective death certification analysis of acromegaly reported in 1970 by Wright et al. They showed a threefold increase in respiratory mortality in both sexes. We considered that if the lungs were to increase in volume by an increase in alveolar size it might be possible to demonstrate disturbed pulmonary function suggestive of emphysema, and the discrepancy between radiographic TLC and helium dilution TLC was suggestive. However, there was no physiological evidence to support this thesis, and radiographic emphysema was detected in only one female in whom pulmonary function was normal. After pneumonectomy, for example, the contralateral lung increases up to 40% in volume and there is no evidence to suggest that morphological emphysema develops (Ogilvie et al., 1963; Dunnill, 1965). The normal values for serum alpha 1 antitrypsin exclude changes in the serum concentration of this protein induced by HGH excess as a potential aetiological factor for emphysema.

Otorhinolaryngologists have recognised for many years that laryngeal structure and the upper airway are altered in acromegaly (Chappell, 1896; Jackson, 1918; Grotting and Pemberton, 1950; Siegler, 1952; Bhatia et al., 1966) and Kitahata pointed out in 1971 the dangers of anaesthesia in
acromegaly. There is prognathism, a large floppy tongue, and an enlarged larynx with congested mucosa and thickened laryngeal tissues, producing a small aperture between the vocal cords. It also is estimated that one-quarter of subjects with acromegaly have an enlarged thyroid gland which may be retrosternal and compress the trachea (Mukhtar et al., 1971). Some of these case reports describe acromegalics with a hoarse voice, breathlessness, and stridor relieved by subsequent tracheostomy, and in the case to be demonstrated by Chappell (1896) the patient suddenly died with respiratory arrest.

We looked for evidence of upper airway narrowing by comparing expiratory and inspiratory flow rate ratios (Simonsson and Malmberg, 1964), and unusually high values were found in six (30%) acromegalics, two females and four males. It would appear that these patients showed evidence of upper airway obstruction and that progression of the disorder could lead to a sudden respiratory death. Three of these subjects consented to indirect laryngoscopy, and in all three there was evidence of upper airway changes attributable to acromegaly.

We could not demonstrate any correlation between the level of growth hormone and the size of the subject's lungs, or laryngeal abnormalities. This accords with the findings of Aloia et al. (1973), who found no correlation between growth hormone levels and other parameters of acromegaly. The lung volumes in acromegaly, however, should be contrasted with hypopituitarism in which Jain et al. (1973) found that the TLC in both sexes was reduced by about 20%.

It is always difficult to estimate the duration of acromegaly as judged by the patient, but Tables 1 and 2 suggest that in men large lung volumes are associated with long duration of symptoms and in both sexes upper airway narrowing is more likely to be found in the presence of a long history.

In the long term it would be of interest to study the effects on the lung volumes and the laryngeal abnormalities of surgery, radiotherapy, and medical treatment directed at reducing the systemic effects of growth hormone. The upper and lower airways as well as the lungs should be included in the parameters to be considered when the management of an acromegalic is under discussion (British Medical Journal, 1974).

We thank Dr. W. T. Taylor, Dr. B. A. Walker, and the late Dr. V. K. Summers for referring patients and Miss D. Pollard and her staff for performing the lung function tests.

References


Cushing, H. and Davidoff, L. M. (1927). The pathological findings in four autopsied cases of acromegaly with a discussion of their significance. Monographs of the Rockefeller Institute for Medical Research, 22.

Pulmonary function in acromegaly


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