

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 acromegalics 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 acromegalics 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 radioimmunoassay 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 (TL_{CO}) 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 radioimmunoassay (Boehringerwerke, 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 acromegalics, 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

Subject	Age (yr)	Duration of disease (yr)	Fasting growth hormone ($\mu\text{g/l}$)	Forced vital capacity % pred.	Forced expiratory volume % pred.	Residual volume % pred.	Total lung capacity % pred.	Transfer factor % pred.	Krogh's permeability constant (K_{CO}) % pred.	MEFR/MIFR ratio
PS	25	3	50	136	109	96	111	108	122	1.0
JC	46	2	80	116	106	98	104	109	111	1.6
BM	38	1	15	120	112	100	109	99	96	2.0
DD	44	14	55	110	81	124	110	71	62	2.5
SA	31	1	20	100	104	93	96	69	80	1.6
EM	47	19	80	146	137	136	141	100	96	3.0
RC	52	32	58	117	96	105	115	103	86	2.0
WJ	49	30	36	113	113	119	112	109	91	1.0
n=8										
Mean	41.5	12.75	49.2	119.8	107.3	108.9	112.3	96.0	93.0	
P obs. v pred.	—	—	—	< 0.01	> 0.05	> 0.05	< 0.05	> 0.05	> 0.05	

Table 2 Pulmonary function in 16 females with acromegaly

Subject	Age (yr)	Duration of disease (yr)	Fasting growth hormone (μg/l)	Forced vital capacity % pred.	Forced expiratory volume % pred.	Residual volume % pred.	Total lung capacity % pred.	Transfer factor % pred.	Krogh's permeability constant (Kco) % pred.	MEFR MIFR ratio
AM	66	2	80	100	85	116	107	94	87	1.6
TS	55	1	40	94	98	90	90	102	125	1.6
GJ	53	9	40	109	100	114	106	147	136	1.3
VR	48	8	40	117	111	94	103	76	75	1.3
ML	67	2	80	103	92	100	103	128	128	1.0
WJ	50	1	77	132	122	62	100	109	120	1.0
LL	35	7	10	123	104	101	108	97	106	2.0
KS	22	2	25	106	87	28	76	75	110	1.6
JB	42	4	8	130	132	100	118	91	89	1.2
KM	54	10	0	87	64	103	87	64	80	1.0
TT	56	3	5	98	77	158	120	104	95	1.5
MM	34	7	100	111	105	82	97	79	100	2.0
n=12										
Mean	48	4.8	42	109	98.1	95.7	101.3	97.2	104.3	
P obs. v pred.	—	—	—	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	
EW	48	9	80	87	66	160	106	61	57	0.8
DR	65	4	20	78	53	113	88	79	92	0.3
KH	58	2	30	104	88	76	89	84	96	0.9
MS	57	2	30	57	44	100	70	76	109	0.7

existing pulmonary disease and were significantly increased above the normal for this laboratory (1.5) in two females and four males.

RADIOGRAPHIC 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 T.L.C. exceeds predicted values in males but not in females.

BLOOD ANALYSES

The alpha 1 antitrypsin 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 acromegalics

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

Subject	Angle of kyphosis (degrees)	Posterior vertebral scalloping	Emphysema	Total lung capacity % pred.	
				X-ray	Helium
Males					
JC	22	—	—	118	104
SA	26	—	—	100	96
RC	32	—	—	114	115
WJ	30	—	—	132	112
Mean				118	107
P obs. v pred.				< 0.05	< 0.05
Females					
ML	38	—	+	121	103
WJ	20	—	—	89	100
LL	23	—	—	105	108
KS	28	—	—	86	76
JB	35	—	—	108	118
MM	28	—	—	88	97
Mean				100	100
P obs. v pred.				> 0.05	> 0.05
With significant kyphosis					
Males					
PS	93	+	—	110	111
BM	43	—	—	103	109
DD	60	+	—	156	110
EM	69	+	—	162	141
Females					
AM	60	—	—	145	107
TS	85	—	—	154	90
GJ	60	—	—	108	106
VR	40	—	—	117	103
KM	53	—	—	117	87
TT	57	—	—	101	120

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 acromegalics 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 acromegalics 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 Toppell *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 acromegalics 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 TL_{Co} and K_{Co} 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).

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References

- Aloia, J. F., Field, R. A., and Kramer, S. (1973). Treatment of acromegaly. *Archives of Internal Medicine*, **131**, 509–515.
- Angus, G. E. and Thurlbeck, W. M. (1972). Number of alveoli in the human lung. *Journal of Applied Physiology*, **32**, 483–485.
- Astwood, E. B. (1955). Growth hormone and corticotrophin. In *The Hormones*, edited by G. Pincus and K. V. Thimann, vol. 3, pp. 235–308. Academic Press, New York.
- Barnhard, H. J., Pierce, J. A., Joyce, J. W., and Bates, J. H. (1960). Roentgenographic determination of total lung capacity: a new method evaluated in health, emphysema and congestive heart failure. *American Journal of Medicine*, **28**, 51–60.
- Bartlett, D., Jr. (1971). Postnatal growth of the mammalian lung: influence of excess growth hormone. *Respiration Physiology*, **12**, 297–304.
- Bedell, G. N., Marshall, R., DuBois, A. B., and Comroe, J. H., Jr. (1956). Plethysmographic determination of the volume of gas trapped in the lungs. *Journal of Clinical Investigation*, **35**, 664–670.
- Bernstein, L., D'Silva, J. L., and Mendel, D. (1952). The effect of the rate of breathing on the maximum breathing capacity determined with a new spirometer. *Thorax*, **7**, 255–262.
- Bhatia, M. L., Misra, S. C., and Prakash, J. (1966). Laryngeal manifestations in acromegaly. *Journal of Laryngology and Otology*, **80**, 412–417.
- Bradford, D. S., Moe, J. H., Montalvo, F. J., and Winter, R. B. (1974). Scheuermann's kyphosis and roundback deformity. *Journal of Bone and Joint Surgery*, **56A**, 740–758.
- British Medical Journal (1974). Assessment and management of acromegaly (Editorial). *British Medical Journal*, **4**, 549–550.
- Brody, J. S., Fisher, A. B., Gocmen, A., and DuBois, A. B. (1970). Acromegalic pneumomegaly lung growth in the adult. *Journal of Clinical Investigation*, **49**, 1051–1060.
- Chappell, W. F. (1896). A case of acromegaly with laryngeal and pharyngeal symptoms. *Journal of Laryngology Rhinology and Otology*, **10**, 142.
- Cotes, J. E. (1968). *Lung Function: Assessment and Application in Medicine*, 2nd edition. Blackwell, Oxford.
- 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**.
- Daughaday, W. H. (1968). The adeno-hypophysis. In *Textbook of Endocrinology*, edited by R. H. Williams, 4th edition, vol. 2, p. 27. Saunders, Philadelphia.

- Dunnill, M. S. (1962). Postnatal growth of the lung. *Thorax*, **17**, 329–333.
- Dunnill, M. S. (1965). Quantitative observations on the anatomy of chronic non-specific lung disease. *Medicina Thoracalis*, **22**, 261–274.
- Gordon, D. A., Hill, F. M., and Ezrin, C. (1962). Acromegaly: a review of 100 cases. *Canadian Medical Association Journal*, **87**, 1106–1109.
- Grotting, J. K. and Pemberton, J. deJ. (1950). Fixation of the vocal cords in acromegaly. *Archives of Otolaryngology*, **52**, 608–617.
- Jackson, C. (1918). Acromegaly of the larynx. *Journal of the American Medical Association*, **71**, 1787–1789.
- Jain, B. P., Brody, J. S., and Fisher, A. B. (1973). The small lung of hypopituitarism. *American Review of Respiratory Disease*, **108**, 49–55.
- Kitahata, L. M. (1971). Airway difficulties associated with anaesthesia in acromegaly. *British Journal of Anaesthesia*, **43**, 1187–1190.
- Lang, E. K. and Bessler, W. T. (1961). The roentgenologic features of acromegaly. *American Journal of Roentgenology*, **86**, 321–328.
- Loyd, H. M., String, T., and DuBois, A. B. (1966). Radiographic and plethysmographic determination of total lung capacity. *Radiology*, **86**, 7–14.
- Mukhtar, E., Alexander, L., Wilkinson, R., Appleton, D., and Hall, R. (1971). Thyroid function in acromegaly. *Lancet*, **2**, 279–283.
- Murray, R. O. and Jacobson, H. G. (1971). *The Radiology of Skeletal Disorders*. Churchill Livingstone, Edinburgh and London.
- 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*, **30**, 1–17.
- Ogilvie, C., Harris, L. H., Meecham, J., and Ryder, G. (1963). Ten years after pneumonectomy for carcinoma. *British Medical Journal*, **1**, 1111–1115.
- Schwartz, E., Echemendia, E., Schiffer, M., and Panariello, V. A. (1969). Mechanism of estrogenic action in acromegaly. *Journal of Clinical Investigation*, **48**, 260–270.
- Siegler, J. (1952). Acromegaly associated with laryngeal obstruction. *Journal of Laryngology and Otology*, **66**, 620–621.
- Simon, G. (1971). *Principles of Chest X-ray Diagnosis*, 3rd edition. Butterworths, London.
- Simonsson, B. G. and Malmberg, R. (1964). Differentiation between localized and generalized airway obstruction. *Thorax*, **19**, 416–419.
- Steinbach, H. L., Feldman, R., and Goldberg, M. B. (1959). Acromegaly. *Radiology*, **72**, 535–549.
- Toppell, K. L., Atkinson, R., and Whitcomb, M. E. (1973). Lung growth in acromegaly. *American Review of Respiratory Disease*, **108**, 1254–1258.
- Van Ganse, W. F., Ferris, B. G., Jr., and Cotes, J. E. (1972). Cigarette smoking and pulmonary diffusing capacity. (transfer factor). *American Review of Respiratory Disease*, **105**, 30–41.
- Wiedemann, E. and Schwartz, E. (1972). Suppression of growth hormone—dependent human serum sulfation factor by estrogen. *Journal of Clinical Endocrinology and Metabolism*, **34**, 51–58.
- Wright, A. D., Hill, D. M., Lowy, C., and Russell Fraser, T. (1970). Mortality in acromegaly. *Quarterly Journal of Medicine*, **34**, 1–16.

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