Large lungs and growth hormone: an increased alveolar number?


ABSTRACT: Previous physiological studies suggest that increased lung growth in patients with acromegaly is associated with either a normal or above normal pulmonary transfer factor. These findings can be interpreted to suggest either alveolar hypertrophy or hyperplasia as the mechanism for lung growth in this condition. Since the ventilated airspaces retain normal elastic properties, we wanted to determine whether the mechanism for lung growth in acromegaly is the result of an increased alveolar number rather than size.

Measurements of pulmonary distensibility (K) (an index of alveolar size), elastic recoil, single-breath carbon monoxide transfer factor and carbon monoxide transfer coefficient (KCo), pulmonary capillary blood volume and alveolar membrane diffusing capacity, together with chest width, were compared in nonsmoking, acromegalic and normal men and women, with and without an increased lung size.

Pulmonary transfer factor was normal for all groups studied, regardless of lung size. However, KCo was inversely related to total lung capacity (% predicted) for all subjects and KCo (% predicted) was inversely related to chest width in men. Pulmonary capillary blood volume (% predicted) was inversely related to total lung capacity (% predicted) for subjects with large lungs. Pulmonary distensibility (K), membrane diffusing capacity and elastic recoil were within the normal range.

These findings suggest normal alveolar size, alveolar membrane surface area and mechanical function in subjects with large lungs. They also suggest that KCo may not be a reliable guide to the interpretation of the mechanism of lung growth in individuals with disproportionately large lungs, and may be reduced because not all the alveoli are perfused. The normal values for pulmonary distensibility found in all our individuals with large lungs, including acromegalics, suggest that lung growth has been achieved by an increased alveolar number rather than size. However, morphometric studies of the lungs of nonsmoking, acromegalic subjects without lung disease, are required to substantiate this finding.

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In view of the above findings and our own observations that $K_{CO}$ is reduced both in normal and acromegalic subjects with large lungs, we hypothesized that lung size in acromegaly is achieved through a process of alveolar hyperplasia rather than hypertrophy.

In this study, we have re-examined other possible mechanisms for the increased lung size in subjects with acromegaly, exploring both transfer factor, pulmonary distensibility (K), pulmonary capillary blood volume and membrane diffusing capacity. For comparison, we also studied the lung function and physical characteristics of healthy male and female subjects with and without an increased lung size.

**Subjects**

Eight male and six female lifelong nonsmoking acromegalic subjects with large lungs were studied. They self-selected from a much larger cohort (n=55) of acromegalis, the majority of whom were smokers. All subjects used in the study were lifelong nonsmokers and without history of chronic cough or recurrent respiratory illness. Ten male and six female control subjects (TLC <110% pred) of unknown cause were also studied. They were members of either the medical, technical or student body of our institution, and were initially screened for determination of their lung size (VC, TLC) and placed in the relevant groups based entirely on lung size, before any other lung function test had been performed. The difficulty of finding a sufficient number of individuals with large lungs limited our ability to match our groups for age.

None of the subjects were engaged in any sort of intensive athletic training, although most of the healthy male subjects took some form of regular exercise, e.g. running, tennis, basketball, cycling. All subjects were informed of the experimental requirements prior to attendance and signed consent forms. All were aware that they could discontinue testing at any time. The diagnosis of acromegaly was based on the characteristic clinical findings and an elevation in the fasting serum growth hormone level measured during an oral glucose tolerance test. All subjects were out-patients at the time of the study, and all were in a clinically stable state. None of subjects chosen for inclusion in this study had significant kyphosis or clinical or radiological evidence of pulmonary hypertension.

**Methods**

**Height, weight, body composition, and pulmonary function at rest**

Anthropometric measurements, including height, weight, and chest width at TLC measured at the xiphoid process were obtained. Relative sitting height (RSH) was derived from an estimation of sitting height divided by standing height in each subject. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV$_1$) were measured using a model S Vitalograph bellows spirometer, documented at body temperature and pressure saturated with water vapour (BTPS). TLC and relaxed vital capacity (VC) were measured in a body plethysmograph (Gould 2800). Maximal inspiratory (MIP) and maximal expiratory (MEP) mouth pressures were recorded from residual volume (RV) and total lung capacity, respectively using a hand held pressure gauge. All of the above tests have been described in detail previously [5, 6].

**Pulmonary distensibility**

Pulmonary distensibility (K) and elastic recoil were estimated according to the methods of Colebatch et al. [7]. Static pressure-volume (P-V) data were generated during several interrupted deflations from TLC to FRC, with the subject seated inside an Emerson volume body plethysmograph. Transpulmonary pressure was measured using an oesophageal balloon catheter one metre long (gas volume 0.5–1.0 ml) and a Hewlett Packard differential pressure transducer 267B. After measurement of TLC and maximal elastic recoil, subjects relaxed against the occluded mouthpiece, which allowed pressure and volume just below TLC to be recorded with sufficient data points to provide an entire fitted curve. Up to five P-V curves, each with 7–10 data points, were pooled to produce a final curve. An exponential function of the form: $V = A - Be^{-Kp}$, where V is lung volume, p is static elastic recoil pressure, and A, B and K are constants, was fitted to the P-V data from TLC to a lower limit not less than 50% of TLC, and analysed by computer. The exponential constant, K, describes the shape of the P-V curve independent of TLC [7].

**Pulmonary capillary blood volume (Vc) and membrane diffusing capacity (Dm) at rest**

This test was performed according to the method of Roughton and Forster [8] using a modified single-breath technique [9], which has been shown in this laboratory to give similar results to those obtained using the conventional method [4]. This modification consisted of a single-breath $T_{LCO}$ measured in duplicate at two different inspired oxygen concentrations supplied by demand values from gas cylinders. These cylinders contained: 1) 0.3% CO, 10% He, 21% O$_2$ and the balance N$_2$, and 2) 0.3% CO, 10% He and 90% O$_2$.

A HP 47404A (Hewlett Packard) single-breath transfer system was used, which incorporated the Jones-Meade convention for breathholding time. Between each of the two gas mixtures, the helium and carbon monoxide analysers were recalibrated using the appropriate gas concentrations. The subjects breathed room air tidally for several breaths and then exhaled slowly to RV. At RV the subject inhaled the test gas rapidly to TLC and breathedhold for 10 s, then exhaled as fast as possible. The first 800 ml of expired gas was discarded as dead space gas, and the next litre retained in the alveolar sample bag which
was fitted with a side-arm and three-way tap. A correction was made to the inspired volume to allow both for the anatomical and instrument dead spaces (0.2 L). After each TLCO manoeuvre, a 20 ml aliquot of expired gas was sampled (using several wash-outs of the syringe). The final sample was analysed for oxygen and carbon dioxide tensions using a blood gas analyser (Corning 175, Medical, MA, USA). These values were taken as an estimate of alveolar oxygen and carbon dioxide tensions (PaO₂ and PaCO₂). The rate of CO uptake by the red blood cells (1/φ) was calculated for each measurement of PaO₂, using the equation [10]:

\[ 1/\phi = P_{A, O_2} \times 0.0057 + 0.10 \]  

(1)

Because of the multiple testing, carboxyhaemoglobin levels were estimated for each TLCO manoeuvre, following an estimation of alveolar CO using the micro smoker-lyser (Bedfont Tech. Instr., Sittingbourne, Kent, UK). The decrease in TLCO due to back pressure was estimated according to the equation of Cardigan et al. [11] (Eq. 2), and this value was added to the observed TLCO.

\[ \% \, TLCO \, decrease = 0.036 \, \text{ml CO-min}^{-1} \text{kPa}^{-1} \times \text{COHb\%} \]  

(2)

Pulmonary capillary blood volume (Vc) was calculated as follows:

\[ 1/Vc = 1/TLCO \, \text{high } P_{O_2} - 1/TLCO \, \text{low } P_{O_2} \]  

\[ 1/\phi \, \text{high } P_{O_2} - 1/\phi \, \text{low } P_{O_2} \]  

(3)

Membrane diffusing capacity was calculated as follows:

\[ 1/Dm = 1/TLCO \, \text{low } P_{O_2} - (1/\phi \, \text{low } P_{O_2} \times 1/Vc) \]  

(4)

Corrections of the observed TLCO,sb at rest and during steady-state exercise for variation in PaO₂ were made according to the equation of Kannan and Crapo [12]. TLCO varies inversely with PaO₂; TLCO,sb corrected = TLCO (measured) \times [1.0 + 0.0035 (PaO₂ - 120)]. When PaO₂ was <120, this equation was rearranged accordingly.

**Single-breath estimation of TLCO and KCO during steady-state exercise**

The transfer capacity of the lungs (TLCO, sb) during exercise was measured by the technique of Neville et al. [13]. Subjects pedalled for 3 min at 25 W without a noseclip or mouthpiece. At the end of this period (with noseclip on) they were attached to the TLCO,sb apparatus mouthpiece and performed a single-breath manoeuvre, whilst still exercising. At the end of the 7–10 s breathhold they expired forcibly, came off the mouthpiece and rested for 5 min. A 20 ml syringe of alveolar gas was sampled, as described previously, for estimation of PaO₂. Exercise was continued in 25–50 W increments (each for 3 min) up to a maximum of 150 W, depending on the capacity of the subject. KCO was calculated as TLCO, sb/VA BTPS at each workload. VA is the alveolar volume measured by helium dilution during a 10 s breathhold at full inspiration. TLCO, sb at each workload was corrected for CO backpressure and PaO₂ tension as described earlier.

**Haemoglobin**

Correction of TLCO, sb for variation in haemoglobin (Hb) concentration was not made either at rest or during exercise. We used the values of ROCA et al. [14] for resting normal TLCO, sb values derived from a regression equation which omitted this correction. This predicted resting values of ROCA et al. [14] were, however, similar to those of KENDRIK and LASZLO [15], who did standardize their TLCO, sb values to a Hb level of 146 g·L⁻¹. We measured Hb concentration in four of our normal females with the largest lungs, and found a mean Hb level of 139±4 g·L⁻¹. Calculations to correct for Hb in these subjects revealed a 2.5% underestimation in TLCO, sb and KCO in these women, insufficient to explain the low KCO values found in this group with large lungs.

**Closing volume (CV%VC) and ventilation distribution**

These indices of lung function were measured in the acromegalic subjects using the single-breath nitrogen test, as modified by ANTHONISEN et al. [16], and expressed as a percentage of predicted values [17]. Delta N₂ was calculated from the single-breath nitrogen wash-out curve as the percentage rise of nitrogen per litre of expired gas, 800–1,200 ml after the start of expiration (∆N₂%·L⁻¹). Expiratory flow rates were kept between 0.3–0.5 L·s⁻¹. A 200 ml dead space containing room air separated the patient from the 100% O₂ used for the test; this was done in order to preferentially prime the apical lung zones with 80% N₂, so that the point of airway closure could be more easily differentiated from the slope of phase three (alveolar plateau).

**Statistical methods**

Analysis of variance was used to determine between group differences of continuous variables shown in the tables. Duncan’s multiple range test was used for post hoc comparisons, to determine statistical differences between groups at the p less than 0.05 level, using the pooled variance [18]. The degree of association between variables shown in the figures were computed using Pearson’s correlation coefficient. Multiple regression was used to determine the significance of gender or group in the models, and where these were not significant, data for males and females, or for different groups, were included together. Repeated measures analysis of variance was used to assess between group differences in changes in KCO and TLCO during steady-state exercise.

**Predicted values**

The normal values used to predict spirometric lung function, maximal inspiratory and expiratory mouth pressures, lung volumes, K and elastic recoil pressures [7] have
been reported in detail previously [5, 6]. Regression equations of Burri et al. [4] (based on TLC) were used to predict pulmonary capillary blood volume (Vc) and membrane diffusing capacity (Dm) at rest. We predicted Vc on the basis of TLC and not body surface area (BSA), in order to show that in large lungs the Kco is low because not all the alveoli are perfused. Normal values used for predicting exercise Tl,co,sh and Kco were from Kendrick and Laszlo [15].

**Results**

Table 1 shows the age, height, weight, relative sitting height, chest width and serum growth hormone levels for the male and female groups, respectively. In table 1, the acromegalic male subjects (Group 3) were significantly older than either the male subjects with normal sized lungs (Group 1) or the male subjects with increased lung size (Group 2). There was no significant difference in either standing height or relative sitting height between the three groups studied. The acromegalic males (Group 3) were both heavier and had wider chests than Group 1 with a normal TLC. Chest width at TLC for Groups 1 and 2 were not statistically different. In table 1, the acromegalic females (Group 3) were significantly older than either Group 1 (normal subjects with a normal TLC) or Group 2 (normal subjects with an increased TLC); Group 2 with an increased TLC were older than Group 1 with a normal TLC. There was no significant difference in height, chest width, weight, or relative sitting height between these three groups.

Mean serum insulin-like growth factor (IGF-1) levels were measured in the acromegalic subjects only. Serum IGF-1 levels were approximately double the predicted value for women and treble the predicted value for men, with a wide standard deviation was observed (females 78 (37) nmol·L⁻¹, males 139 (79) nmol·L⁻¹; predicted <45 nmol·L⁻¹).

**Lung volumes, spirometry, Tl,co,sh, Vc, Dm**

Mean subdivisions of lung volume, spirometric function, Tl,co,sh, Kco, Vc and Dm are reported in table 2.

Because of the differences in age between the groups, percentages of the predicted values were used in analysis. For males, VC% pred for the acromegalic males (Group 3) was significantly larger than VC% pred for Groups 1 and 2 (control males with and without an increased TLC), and VC% pred for the males with an increased TLC (Group 2) was significantly bigger than VC% pred for the males with a normal TLC (Group 1). Similar results were obtained when TLC% pred was compared between the three groups. There was no significant difference between FEV₁/FVC% pred, Dm% pred or Tl,co% pred for the three groups studied. Transfer coefficient (Kco% pred) for Group 1 (males with a normal TLC) was found to be significantly greater than in Groups 2 and 3 (males with an increased TLC and the acromegalic males). Pulmonary capillary blood volume (Vc% pred) for the males with a normal TLC (Group 1) was significantly greater than for the acromegalic males (Group 3), despite their increased lung size.

For females, VC% pred was similar for Groups 2 and 3 (normal females with increased TLC and acromegalic females with big lungs), and both these groups had significantly bigger VC% pred than Group 1 (females with normal TLC). Similar results were obtained for TLC % pred. There was no significant difference for either FEV₁/FVC% pred, Tl,co% pred or Vc% pred for the three groups studied. Kco% pred was significantly bigger in Group 1 with the normal TLC than in either the females with increased TLC (Group 2) or the acromegalic females (Group 3), and a similar result was obtained for Dm% pred.

**Lung mechanics, pulmonary distensibility (K) and elastic recoil**

Mean values expressed as % of predicted are shown in table 3. In the male groups, there was no significant difference for either K, elastic recoil at maximal inspiration (Pel,60) or elastic recoil at 60% of TLC (Pel,MI), for the three groups studied. In the female groups, similar results were obtained. The distribution of the original pressure volume data about the derived curve (mean residual variance) and the ratio A/TLC% (a test of the validity of the exponential model) are reported as

<table>
<thead>
<tr>
<th>Male Characteristics</th>
<th>Females Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td><strong>Group 2</strong></td>
</tr>
<tr>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Age yrs</strong></td>
<td>32 (11.3)</td>
</tr>
<tr>
<td><strong>Height cm</strong></td>
<td>180 (6.7)</td>
</tr>
<tr>
<td><strong>Weight cm</strong></td>
<td>80 (9.6)</td>
</tr>
<tr>
<td><strong>RSH</strong></td>
<td>0.52 (0.01)</td>
</tr>
<tr>
<td><strong>Chest width at TLC cm</strong></td>
<td>30.4 (2.4)</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd). RSH: relative sitting height (sitting height/standard height); ns: nonsignificant; TLC: total lung capacity.
Table 2. – Lung volumes, spirometry, diffusing capacity and its subdivisions in male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>TLC n=10</td>
<td>TLC n=10</td>
</tr>
<tr>
<td>TLC % pred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC L</td>
<td>5.72 (0.8)</td>
<td>6.51 (0.6)</td>
</tr>
<tr>
<td>VC % pred</td>
<td>104 (7)</td>
<td>117 (5)</td>
</tr>
<tr>
<td>TLC L</td>
<td>7.39 (0.7)</td>
<td>8.56 (0.8)</td>
</tr>
<tr>
<td>TLC % pred</td>
<td>103 (4)</td>
<td>116 (3)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>81 (4)</td>
<td>78 (6.0)</td>
</tr>
<tr>
<td>FEV1/FVC % pred</td>
<td>98 (5)</td>
<td>96 (6)</td>
</tr>
<tr>
<td>TLC CO mmol·min⁻¹·kPa⁻¹</td>
<td>12.9 (1.8)</td>
<td>13.1 (1.7)</td>
</tr>
<tr>
<td>TLC CO % pred</td>
<td>102 (14)</td>
<td>100 (13)</td>
</tr>
<tr>
<td>KCO mmol·min⁻¹·kPa⁻¹·L⁻¹</td>
<td>1.79 (0.12)</td>
<td>1.58 (0.15)</td>
</tr>
<tr>
<td>K CO % pred</td>
<td>94 (6)</td>
<td>84 (8)</td>
</tr>
<tr>
<td>VC ml</td>
<td>89 (16)</td>
<td>83 (18)</td>
</tr>
<tr>
<td>VC ml % pred</td>
<td>104 (17)</td>
<td>88 (19)</td>
</tr>
<tr>
<td>Dm mmol·min⁻¹·kPa⁻¹</td>
<td>38 (12)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Dm % pred</td>
<td>133 (42)</td>
<td>133 (36)</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd) and as % predicted (sd). VC: vital capacity; TLC: total lung capacity; FEV1/FVC%: forced expiratory volume in one second; TLC,CO,sb: single-breath estimate of transfer factor of the lung for carbon monoxide at rest; KCO: carbon monoxide transfer coefficient (TLC,CO STPD/alveolar volume (VA) BTPS); Vc: pulmonary capillary blood volume; Dm: alveolar/capillary membrane diffusing capacity; NS: nonsignificant; BTPS: body temperature and pressure saturated with water vapour; STPD: standard temperature and pressure dry.

Table 3. – Alveolar distensibility (K) and elastic recoil in male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>K kPa⁻¹</td>
<td>1.20 (0.30)</td>
<td>1.29 (0.30)</td>
</tr>
<tr>
<td>% pred</td>
<td>94 (22)</td>
<td>103 (28)</td>
</tr>
<tr>
<td>Pet max kPa</td>
<td>3.91 (1.04)</td>
<td>3.84 (0.83)</td>
</tr>
<tr>
<td>% pred</td>
<td>101 (24)</td>
<td>99 (25)</td>
</tr>
<tr>
<td>Peso60 kPa</td>
<td>0.71 (0.22)</td>
<td>0.77 (0.14)</td>
</tr>
<tr>
<td>% pred</td>
<td>109 (23)</td>
<td>117 (31)</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd) and as % predicted (sd). K: pulmonary distensibility; Pet max: elastic recoil of the lung at maximal inspiration; Peso60: elastic recoil of the lung at 60% of maximal inspiration; NS: nonsignificant.
follows. For the acromegalic men, mean residual variance values were 1.78±1.7%, and A/TLC% values 104.5±2.9%. For the acromegalic women these same values were 3.15±1.4% and 102.3±1.4%, respectively. For the males and females with TLC <110% of predicted, these values were 2.53±1.3% and 101.4±2.6%, and 1.57±1.2% and 102.7±3.1%, respectively. For the males and females with TLC >110% of predicted, 2.29±1.5% and 99.0±5.3%, and 1.1±0.6% and 102.7±3.1%, respectively. Mean maximal inspiratory mouth pressures from residual volume (MIP from RV%) and mean maximal expiratory mouth pressures from TLC (MEP from TLC%) both for the male (MIP 112±31%, MEP 113±41%) and female (MIP 92±20%, MEP 106±21%) acromegalic subjects were normal. Values for both ventilation distribution (ΔN2%·L-1) and closing volume (CV %VC) for male and female acromegalic subjects were within the normal limits (males ΔN2%·L-1 72±29%, CV %VC 121±24%, and females ΔN2%·L-1 87±31% and CV %VC 130±18%). Not all subjects were either willing or able to swallow the oesophageal balloon catheter. In table 3, the number of subjects in each group tested for pulmonary distensibility (K) are indicated.

Relationship between lung function and physical characteristics for all groups combined

The relationship between Kco, Vc% pred Dm and lung size are shown in figures 1–3. There was an inverse relationship between lung volume (TLC% pred) and Kco (fig. 1) (r=-0.50; p<0.0002). A similar correlation was obtained when Vc% pred was plotted against TLC% pred (r=-0.57; p<0.0001), Vc% pred diminish as lung size (TLC% pred) increased above 100% (fig. 2). Figure 3 shows the relationship between lung size (TLC) and membrane diffusion capacity (Dm). As TLC increased, membrane diffusion capacity increased (r=0.45; p<0.003). However, in nine out of 11 acromegalic subjects, Dm fell below regression. When sex was included as a variable in the regression shown in figures 1 and 3, it was
not a significant factor, therefore, data for both sexes have been pooled.

Figure 4 shows the relationship between absolute pulmonary capillary blood volume (Vc) and lung size (TLC) for subjects with a TLC <110% pred (broken line) and for subjects with a TLC >110% pred (solid line). The slope of the regression line for 16 subjects with a TLC <110% pred was the same as that found by Burri et al. [4] in their study of 34 normal subjects using the conventional method for estimation of Vc and Dm. The regression line for subjects with lungs larger than 110% pred was of a similar slope, but was displaced to the right.

Fig. 5. – Relationship between single-breath transfer factor (TL,CO,sb), diffusion coefficient (KCO) and work (W) for healthy males and females with and without an increase in lung size, expressed as total lung capacity (TLC). Each bar represents ± SD; n: numbers of subjects exercised. Isobars have been removed from the predicted slopes (dotted lines). - - -: predicted; ––: males with normal TLC (n=8); ——: males with increased TLC (n=8); ——: females with normal TLC (n=5); ——: females with increased TLC (n=10).

Fig. 6. – Relationship between single-breath transfer factor (TL,CO,sb), transfer coefficient (KCO) and workload (W) for male and female acromegalic subjects. Each bar represents ± SD. Isobars have been removed from the predicted slopes (dotted lines). Statistical comparisons were not appropriate. n: number of subjects exercised. - - -: predicted; ——: acromegalic males (n=3); ——: acromegalic females (n=4).
Single-breath transfer factor ($T_{L,CO,SB}$) and transfer coefficient ($KCO$) during steady-state exercise

The relationships between incremental steady-state exercise and $T_{L,CO,SB}$ and $KCO$, respectively, are shown for all groups in figures 5 and 6. In figure 5a, $T_{L,CO,SB}$ for the healthy male subjects with and without an increased TLC (groups 2 and 1) was similar at rest, and during exercise increased by the same amount for all workloads attempted. $KCO$ for the male subjects with a normal TLC was not significantly different from $KCO$ found for the male subjects with an increased TLC. Similar results were obtained for the normal females (fig. 5b) with and without an increased TLC. In the male and female acromegalic subjects with big lungs (fig. 6a and b), both sexes during exercise recruited reserves of $T_{L,CO}$ at the predicted rate, whilst $KCO$ was recruited at a normal rate, albeit at a lower level ($80\%$ pred), similar to the differences between observed and predicted $KCO$ at rest (tables 2).

Discussion

In this study, the increased lung volumes in our patients with acromegaly and controls with large lungs appeared not to be due to a growth in the size of existing alveoli, as suggested previously [2], or to an overdistension of alveoli due to increased values for maximal inspiratory mouth pressure (MIP), but may have resulted from an increased alveolar number in association with increased growth hormone (GH) secretion and with the growth of physically larger chests. We measured pulmonary distensibility $K$, (an index of alveolar size [19]). This test was part of a detailed analysis of mechanical lung function and gas exchange at rest and during exercise, which, importantly, included for comparison groups of normal subjects with and without an increase in lung size. Pulmonary distensibility and elastic recoil were normal for all subjects studied.

The technique of determining alveolar distensibility by applying an exponential function to a static compliance curve has been described previously [7]. The relationship of the exponent K to $Lm$ [19] (a morphometric estimate of the mean size of alveolar airspaces at TLC), the relationship between chest size, alveolar distensibility and alveolar size and number have also been fully discussed previously [5, 6]. Total lung capacity is determined by the number and size of airspaces in the lungs. Alveolar distensibility is not related to alveolar number [19], or to height [20], and is independent of lung size and sex [20]. In intact human subjects, K is an independent determinant of TLC [21], a fact that is difficult to explain unless K reflects airspace size.

In the present study, there was no significant difference in either K or elastic recoil between acromegalic or normal subjects, with or without an increase in TLC, suggesting either: 1) alveolar multiplication and not hypertrophy as the growth mechanism to account for the individuals with large lungs; or 2) alveolar hypertrophy not detectable through the measurement of pulmonary distensibility in the present study. The finding of normal values for elastic recoil in both studies (a simpler procedure to the estimation of K) strongly supports the first hypothesis, that alveolar multiplication was the growth mechanism in the individuals with large lungs. In support of this, HOPPIN and HILDEBRANDT [22] in their general analysis of surface forces and size of airspaces, showed that the surface component of recoil pressure was inversely related to $Lm$ and directly related to the alveolar surface to volume ratio. The strong relationship between $K$ and $Lm$ [$r^2=0.86$ [19]] is, therefore, consistent with surface forces having the predominant influence on lung distensibility. In this study, the normal values for elastic recoil found for all the groups studied suggest that alveolar surface area to volume ratio was similar and, therefore, the alveoli were of similar size. In support of the second hypothesis, it could be argued that there was alveolar enlargement, and this was accommodated by some structural remodelling of connective tissue or surfactant metabolism, such that K was preserved. However, it has been shown that pulmonary distensibility predominantly reflects surface forces. In the excised lungs of rats, cats and dogs tissue, elastic properties (as assessed in saline-filled lungs) had no discernible effect on the distensibility of air-inflated lungs [19]. The composition of surfactant is similar in various species, and the total amount of surfactant correlates well with alveolar surface area, and there is a substantial reserve of surface active material [22].

It could also be argued that if growth hormone excess had resulted in the formation of new alveoli (with a resultant increase in the surface area for gas exchange), $T_{L,CO,SB}$ should have increased in the acromegalic and normal subjects with large lungs. Pulmonary diffusing capacity is the product of its components $Dm$ and $Vc$. Whilst we showed a direct relationship between TCL and $Dm$ for all subjects (fig. 3), the values for $Dm$ tended to be normal for the male and female acromegalic subjects and the Group 2 female subjects despite their increased lung size. In their study, Brody et al. [2] found lung tissue volume to be twice the normal value in five out of six male acromegalics with increased lung size, and suggested that an increase in interstitial tissue might have impeded diffusion. This may explain the normal $Dm$ that we observed for the acromegalic subjects despite evidence for an increased alveolar number (table 2). However, another reason seems plausible: measurement of $Dm$ is dependent on some blood flow to the alveolus; in those subjects with big lungs, where perfusion distances are excessive, peripheral alveoli may be so poorly perfused as to affect $Dm$.

In the present study, pulmonary capillary blood volume percentage predicted ($Vc\%$ pred) and $KCO$ were shown to be inversely related to TLC % pred for all subjects (figs 2 and 1). In addition, TLC% pred was related to chest width in acromegalic men but not women (table 1), due to differences in their thoracic indices [5]. Brody et al. [2] found chest depth and circumference to be increased in acromegaly, and this was also the case in the present study. Since pulmonary capillary blood volume ($Vc$) has been shown to relate to stroke volume, these findings suggest that in sedentary individuals, with
large lungs, a decrease in KCO may result from an increase in the unperfused capillary bed, and the wider or deeper their lungs the lower would be the KCO for a given stroke volume. During exercise, these individuals recruited reserves of KCO at a normal slope but, in most instances, at a reduced absolute level compared to those subjects with normal sized lungs (figs 5 and 6). There is anatomical evidence in the literature to support these findings.

In a study of the effects of growth on the KCO at rest in children and young adults, O'BRODOVICH et al. [3] have shown that KCO decreases with increasing height. Placing their subjects in the supine position resulted in an increase in KCO of up to 27%, more so in the taller subjects; thus, confirming the apex to base vertical gradient in pulmonary blood flow and explaining the lower KCO in taller individuals to be due to a decrease in the ratio of the perfused alveolar surface area to alveolar volume during growth. In this study, however, increasing subject height could only partly explain the decrease in KCO with age [3].

Whilst the gravitationally-induced (top-bottom) distribution of pulmonary blood flow is widely known and understood, the central-peripheral three dimensional distribution of pulmonary blood flow is less so. Using a high resolution single photon emission computerized tomography technique (SPECT), HARIM et al. [23] have demonstrated a gravity independent inequality in pulmonary blood flow in humans and in dogs. The authors argued that regional differences in vascular conductance, independent of gravity and present in individual lobes in man and in dogs in the supine position, may explain this finding; and suggest that flow to a site is inversely related to the distance the blood must travel to reach that specific site. In a more recent manuscript dealing with capillary perfusion patterns in single alveolar walls, it has been observed using in vivo video-microscopy that blood flowing through peripheral alveolar capillary networks in dogs sought a unique and repeatable pattern of vascular segments when the pulmonary arterial pressure was altered in a repeated fashion [24]. The authors interpreted this as demonstrating that pulmonary capillary blood flow sought the pathway of least total resistance, and that the resistance of each segment differed from the resistance of other segments. They observed that alveolar capillary segments perfused during these changes in driving pressure were shorter than the segments that were never perfused. These studies indicate that, during the resting condition, gas exchange is accomplished primarily by the central region of the lungs, and that, during exercise, the perfused and ventilated regions can expand peripherally in a three dimensional fashion, thus allowing considerable reserves for enhancing gas exchange [25].

These studies are consistent with our finding of a normal TL,CO and a reduced KCO in untrained individuals with large lungs at rest. Conversely, trained swimmers have been shown to have a normal KCO at rest, perhaps reflecting their increased stroke volume resulting from training [6]. During exercise, however, trained swimmers can utilize their considerable reserves of gas exchange units before saturation of alveolar capillary reserves would occur. Perhaps, the large lungs of swimmers [26–28], in contrast to the normal lungs of runners [6, 29], really are “built for exercise”. In contrast, we have recently described a case of an active young man (with an increased stroke volume, with small thoracic cage, and subsequent restriction of all subdivisions of lung volumes) reaching a plateau of TL,CO,sb recruitment during exercise [30]. His resting KCO was 140% pred and remained unchanged during exercise. The small lung capacity (TLC 59% pred) with normal distensibility, and the increased stroke volume have combined to produce full recruitment of his limited number of alveoli at rest.

The response to exercise in our subjects with large lungs (figs 5 and 6) showed that these subjects recruited reserves of TL,CO and KCO at the same rate as those with normal lungs, indicating that there were anatomical reserves of pulmonary capillaries available for recruitment, the exact amount probably being limited by the stroke volume (Vc). This implies that the reduced KCO at rest was not a result of abnormal pulmonary capillary density or a reduction in surface area:volume ratio, but rather that there were areas (probably peripheral), where perfusion was either reduced or absent. The authors believe that the normal TL,CO and the low KCO at rest were a reflection of a normal stroke volume emptying into a lung containing an increased number of alveoli.

Whilst it is easier to explain our findings of a low KCO for the normal subjects with an increased lung size on the basis of increased perfusion distances, acromegaly is, however, a disease, and abnormalities in lung perfusion scans [31], and in cardiac size and function [32] in untreated cases have been reported. Most patients have some degree of hypoxaemia, usually subclinical, probably due to ventilation/perfusion mismatching [31]. On the basis of their large lung volumes, some of our acromegalic subjects undoubtedly had this disease for a long time. However, since none had gone untreated, abnormalities in cardiac size and function are unlikely to have contributed to their low KCO.

When there are significant differences in age between study groups, it is sometimes difficult to choose representative predicted values for TL,CO,sb and KCO, because different normal predictions can give different age effects. In our laboratory, we have found the regression equations of ROCA et al. [14] for TL,CO,sb and KCO appropriate for the testing methodology and patient population encompassed in this study (25–54 yrs). In addition, the mean value for TL,CO,sb obtained by BRODY et al. [2] (98% pred) for their acromegalic males (mean age 50 yrs) was very similar to the mean value (101% pred) obtained for the acromegalic males in the present study (mean age 45 yrs). Thus, the predicted values that we used for TL,CO,sb [14] showed similar age effects to those used by BRODY et al. [2] in their study.

In conclusion, the similarities in results between all our subjects with large lungs indicate that, mechanically, acromegalic lungs are essentially normal. The normal values for pulmonary distensibility, FEV1/FVC ratio, TL,CO % pred, Dm% pred, ventilation distribution, and closing volume suggest that physiological estimates of the mechanism of lung growth in acromegaly are
indistinguishable from those observed in other individuals with large lungs. We believe that the Kco was low because not all the alveoli were perfused. The similar values for TL,CO% pred between subject groups of similar height and weight, suggest that resting TL,CO, at least for the untrained, is more a function of BSA and not lung size. We conclude that lung growth in the adult with acromegaly may result from an increase in alveolar number rather than size. This information may have relevance for growth hormone treatment of patients with lung disease, for lung size post-pneumonectomy, and may also be of assistance in the interpretation of lung function data of patients with large lungs. However, morphometric studies of the lungs of nonsmoking acromegalic subjects without lung disease are required to substantiate the interpretation of our findings.

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