**V/Q and alveolar gas exchange in pulmonary sarcoidosis**

A. Eklund*, L. Broman, M. Broman, A. Holmgren

**ABSTRACT:** Eleven patients with pulmonary sarcoidosis of type II or III were investigated with regard to regional distribution of ventilation and perfusion (V/Q), alveolar gas exchange and diffusion limit at rest and during exercise. Lung volumes were 50-65% of normal values. Flow-volume curves indicated obstructive changes. The transfer factor was 75% (range 16-120%) of predicted. Perfusion scintigraphy showed marked defects in 7 out of 11 patients. Radiospirometry showed matching ventilation and perfusion defects and washout of xenon was prolonged. There was a venous admixture at rest of 9%. Arterial oxygen tension (Pao₂) averaged 9.7 kPa. V/Q analyses indicated the presence of a small shunt (1%), regions with low V/Q in 4 out of 11 patients, regions with high V/Q in 5 out of 11 patients and increased wasted ventilation. At rest measured Pao₂ was lower (6.6 kPa) than predicted from the V/Q distribution. During mild supine exercise causing significant dyspnoea, pulmonary vascular resistance rose to abnormal values, 5.2 mmHg·l·min⁻¹·m⁻² BSA. The venous admixture decreased to 5.4%. The shunt was unchanged, as was the perfusion of regions with low V/Q. The regions with abnormally high V/Q disappeared. Measured Pao₂ decreased to 9.1 kPa, while calculated Pao₂ remained unchanged. Thus the P(A-a)O₂ at rest (4.2 kPa) was 70% caused by shunt and V/Q mismatch. During exercise alveolar-arterial pressure difference for oxygen measured P(A-a)O₂ rose further to 5.1 kPa, while calculated P(A-a)O₂ remained unchanged and was only 50% caused by shunt and V/Q disturbances. The difference between calculated and measured Pao₂ indicated significant diffusion limitation both at rest and during mild exercise.

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Sarcoidosis is a multisystem granulomatous disorder characterized by histological evidence of widespread non-caseating epithelioid-cell granulomas [1].

An interstitial pneumonitis consisting of macrophages and lymphocytes infiltrating the alveolar wall seems to be an early sign of sarcoidosis in the lung followed by increasing granuloma formation. Some patients eventually develop fibrosis [2].

Sarcoidosis of the lung is frequently associated with reduction of lung volumes when chest X-ray shows parenchymal infiltrates. Such changes may also be present in the absence of pronounced radiographic changes [3, 4], and are often accompanied by a reduction of the transfer factor (Tl) [4, 5]. This reduction may be larger than expected from the reduction in lung volume. Morphometric analysis of the lung in patients with sarcoidosis [6] implies that thickening of the alveolar blood-air barrier is not responsible for the reduction of Tl. This is in agreement with Finley [7] who suggested that ventilation/perfusion V/Q mismatch could be the major determinant of the reduction of Tl in interstitial lung disease. Sarcoidosis of the lung is not only an interstitial disease, however it also involves the airways both large and small. Thus indices of large airway disease such as airway resistance, and expiratory flow rates and of small airway disease such as closing volume and frequency dependant compliance have been reported abnormal [8]. Obstructive disease has also been reported as a predominant feature of sarcoidosis [9]. Pulmonary vascular obstruction and/or destruction leading to pulmonary hypertension is observed in sarcoidosis especially type III [4]. These abnormalities in ventilation and perfusion may lead to impaired alveolar gas exchange as illustrated by an increased alveolar-arterial (A-a) oxygen pressure difference [4].

The present study was undertaken to quantitate the presence and influence of ventilation perfusion and diffusion disturbances on alveolar gas exchange in patients with lung sarcoidosis types II and III.

**Patients and methods**

**Patients**

Eleven nonsmoking patients (3 women, 8 men) with
endobronchial biopsy-proven sarcoidosis were studied (table 1.). The diagnosis was based on a combination of the clinical history, radiological findings and the presence of non-caseating epithelioid-cell granulomas in endobronchial biopsies and/or a positive Kveim test. Patient number 5 was treated with steroids at the time of the study. Patient 11 had severe pulmonary hypertension and is reported separately.

This study was performed according to the Declaration of Helsinki and formed a part of the routine investigations in our clinics.

Methods

Roentgenographic staging. Classification of the roentgenograms was done according to the following system: type I, bilateral hilar lymphadenopathy (BHL); type II (n=3), parenchymal opacities with BHL; type III (n=8), parenchymal changes without BHL.

Angiotensin-converting enzyme in serum (SACE). SACE activity was measured by the spectrophotometric method of Liberman [10] and the enzyme activity was expressed as U·ml⁻¹ (nmol hippuric acid·min⁻¹·ml⁻¹). Normal values were 8–32 U·ml⁻¹.

Physiological procedures.
1. Working capacity (Wsl, watts). A symptom limited exercise test was performed in a sitting position on a bicycle ergometer. The load was increased in steps of 10 watts every minute until the test was interrupted because of severe dyspnoea in all patients.
2. Electrocardiogram ECG. A twelve lead ECG was recorded at rest. Six chest leads were recorded during the exercise test. The indifferent electrode was placed on the forehead during exercise, (CH-leads).
3. Dynamic spirometry forced expiratory flow rate when x % of forced vital capacity is reached was performed with a Bernstein spirometer connected to an IBM 1800 computer. Normal values were calculated from the equations published by Berglund et al. [11]. Flowvolume curves were plotted from the best forced expiration with the aid of the computer. The curves were analysed with respect to morphology, FEF75, FEF50 and FEF25 and mean expiratory transit time. Normal values were calculated from the regression equations of Cherniak et al. [12].
4. Spirometry. Functional residual capacity (FRC) was determined with a He-dilution method [13]. Normal values were calculated from the regression equations of Berglund et al. [11].
5. Single breath transfer factor for carbon monoxide (Tr.CO) was determined according to Ogilvie et al. [14] with the modifications and reference values of Cotes [15]. Duplicate determinations were used with a reproducibility of better than 7%. The results were also presented as Kco i.e. TlCO·l⁻¹ alveolar volume.
6. Blood gases. Blood samples were withdrawn for

### Table 1 - General data for 11 patients with pulmonary sarcoidosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Disease duration</th>
<th>Disease stage</th>
<th>FRC</th>
<th>HRsl</th>
<th>TLC</th>
<th>Kco</th>
<th>FEV1</th>
<th>FEF%</th>
<th>MVV%</th>
<th>TlCO, TlFIN</th>
<th>TlCO, TFIN</th>
<th>TlCO, TFIN</th>
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SACE: Angiotensin converting enzyme activity in serum; Wsl: Working capacity; Tr.CO: Single breath transfer factor to carbon monoxide; Kco: CO per one alveolar volume; TlCO: Transfer factor; FEV1, FEF%: Forced expiratory volume in one second, MVV%: Maximum voluntary ventilation at a breathing rate of 40 min⁻¹; TlCO, TFIN: All in percent of predicted; TlCO, TFIN: Half time of the initial slope of the Ex-Wash out curve calculated with area/height method.
6. Blood gases. Blood samples were withdrawn for determination of blood gas contents, pressures, P50 and the buffer line for mixed venous blood. They were anticoagulated with heparin or ethylenediaminetetraacetic acid (EDTA) and immediately stored in ice water until analysed, usually within 15 min. O₂ and CO₂ partial pressures and pH were measured with a Micro Autocal pH/blood gas analyser (Instrument Laboratories Inc, Model 613). Oxygen content of blood samples was determined spectrophotometrically with a CO-oximeter (Instrument Laboratories Inc, Model 181) and corrected for dissolved oxygen. P50 was determined according to ABERMAN et al. [16] on mixed venous blood. The blood buffer line was established with a micro-equilibration technique [17].

7. Ventilation was measured with a ventilation monitor and an argon dilution technique (Bourns Inc, Model LS 75) both checked regularly against a dynamic pneumotachograph calibrator [18].

8. Gas analysis. Inspired and expired air were analysed on line for O₂, CO₂, N₂ and Ar with a mass spectrometer (20th Century Electronics, Model 200 Mga) calibrated with gas mixtures analysed with the Scholander technique for N₂, O₂, CO₂ and Ar.

9. Perfusion scintigraphy of the lungs was performed with ⁹⁹ᵐTc-tagged microspheres administered in the supine position. Anterior, posterior and lateral views were obtained with a gamma camera, (Maxicamera, General Electric).

10. Radiospirometry was performed with ¹³³Xe immediately after completion of the perfusion scintigraphy in the same position. A dorsal projection was used. The scintigrams were stored in a DEC GAMMA 11 computer for image processing and calculations. A perfusion scintigram was first stored in the computer. The energy window was shifted to ¹³³Xe and a Tc-Compton scatter picture was stored to be used for background subtraction. 20 mCi ¹³³Xe gas was inhaled in the supine position during resting breathing as a bolus from an oxygen-filled closed spirometer system with a gas flow rectifier and CO₂-scrubber. Data were acquired during the initial 30 s (in 5 s 64×64 frames) and a ventilation scintigram was generated. The patient then rebreathed into the closed spirometer system for 4 min or until an approximate equilibrium was obtained. At this time a volume scintigram was obtained. The patient was then disconnected from the spirometer system and the lungs were washed out with room air. Ventilation was monitored with a vortex flow meter. During the wash out, 64×64 frames were collected every second for 30 s and then every 30 s for a total of 5 min. The wash out period was evaluated with analogue wash-out scintigrams collected between 1–2 and 4–5 min. In the computer analyses the Xe-frames were corrected for non-uniformity, count rate. ⁹⁹ᵐTc-Compton scatter, and chest wall background. Half-time for the initial slope of the wash out curve was calculated using a least squares fit. Half-time for the total 5 min wash out period was calculated with an area/height technique (A/H) assuming a monoeponential relationship. These half times were compared with half-times computed from helium FRC and ventilation during wash out using the equation:

\[ T_{1/2} = \frac{\ln(2)}{0.693} \]

\[ t = \frac{V_A}{FRC_{\text{He}} - VD + \frac{1}{2}VT} \]

where \( t \) is mean transit time (seconds), \( V_A \) is alveolar volume [16], \( V_A = \text{alveolar ventilation (l·min}^{-1}\)), \( FRC_{\text{He}} \) is FRC determined with helium dilution [16], \( \text{P}\text{=anatomical dead space [16], calculated from body weight and age (VD=2.2·weight (kg)+Age (years)) [13], } V_T = \text{tidal volume (l), } V_{\text{tot}} = \text{total ventilation (l·min}^{-1}) \text{ during xenon wash out and } f = \text{respiratory rate (breaths·min}^{-1}) \text{ during xenon wash out, all volumes in } l, \text{ all rates in breaths·min}^{-1}. \text{The calculated half-times for initial slope and A/H were compared with those for } T_{1/2}. \text{The matching of } V, V \text{ and } Q \text{ were also computed for both lungs separately and for three regions in each lung - an upper, a central and a lower, by generating } V/Q \text{ scintigrams.}

**Distribution of V/Q studied with inert gas technique.** The distributions of V/Q were determined using the inert gas technique reported by WAGNER et al. [19]. A mixture of six inert gases (SF₆, ethane, cyclopropane, halothane, ether and acetone) dissolved in saline was infused through a peripheral venous catheter at a rate of 2.9 ml·min⁻¹.

After an equilibration period of 30 min, simultaneous 7.5 ml blood samples were withdrawn from the brachial and pulmonary arteries into heparinized 50 ml matched-barrel glass syringes. Mixed expired gas was collected via a heated valve and mixing box system (55°C). Gas samples were taken with heated (55°C) 20 ml gas-tight Hamilton syringes with a delay after the blood sampling corresponding to the mean transit time of the breathing valve plus mixing box system (volume divided by ventilation). These gas syringes were then stored at 55°C until analysed, to avoid condensation of the water vapour in the syringe which could trap acetone in the gas sample.

Inert gas concentrations were determined with a Perkin Elmer F22 gas chromatograph, equipped with a flame ionization detector (FID) and an electron capture detector (ECD), a single column and a splitter. The 1.5 ml glass or nickel column was packed with Porapac QS, 50/80 mesh. The oven temperature was 130°C and the ECD and FID temperatures were 250°C. The carrier gas (nitrogen) flow was 15 ml·min⁻¹. Standard error of a single determination of SF₆ is 2% in blood and 6% in gas samples. For the remaining gases it is less than 4% in both blood and gas phases [20].

The ratio of arterial to mixed venous (retention, R) and mixed expired to mixed venous (excretion, E) concentrations were calculated. Blood-gas partition coefficients for the six gases were taken from WAGNER et al. [19]. Retention- and excretion-solubility diagrams were constructed. Distributions of blood flow and ventilation on ventilation perfusion ratio (V/Q) were then computed using the enforced smoothing method described by EVANS and
markedly reduced values. These patients had flow-
92.4±23% of predicted. Patients 1, 2, 3, 6, 7 and 11 had
59.2±23% of predicted. Only patient 9 had a normal value.

Marked abnormalities in 7 out of 10 patients, as demonstrated by low V/V quotients and long 133Xe half-times. No regions with high V/V were seen. The T1 IN averaged 43.2 s whilst that of the initial slope and A/H slope of the xenon wash out were 12.3 and 45 s respectively. For further analyses the values for T1 IN (initial slope) for each of six segments of the two lungs (fig. 2). T1 IN of the initial slope is a parameter mainly related to ventilation [22, 23] and the figure illustrates the impairment of gas turn-
in the lungs.

Blood volume, haemoglobin concentration and total haemoglobin were normal, on average 99.0, 99.8 and 89.1% of predicted, respectively.

Single breath transfer factor. Alveolar volume was 75.4% of predicted. Tlco was 72.8 and Kco (Tlco·l-1 alveolar volume) 83% of predicted. Patients 1, 5 and 11 had a Tlco of 24, 11 and 16% respectively. Normal values were found in patients 2 and 9.

Arterial blood gases and acid base balance (table 2). The average arterial Po2 was 9.7 (SD±1.3) kPa. Low values were found in patients 1, 5 and 11, who had 8.9, 7.1 and 5.7 kPa. Nine out of 11 had a pressure below 10 kPa. Arterial Pco2 averaged 5.1±0.4 kPa, 2 out of 11 had a pressure below 4.5 kPa. Arterial pH was 7.42±0.05 units. Three patients had a pH above 7.45 and one below 7.35. Base excess averaged 0.3±3 mmol·l-1.

Central haemodynamics at rest (table 2). The relationship between cardiac output and oxygen uptake was normal at rest. The resting oxygen uptake was on average +18.3% of BMB. The arterio-venous oxygen concentration difference was 45.9±8.7 ml·l-1·min-1, arterial oxygen saturation averaged 93%, the mixed venous oxygen saturation and tension were 72.4±3.8% and 5.2±2.4 kPa, respectively. Heart rate averaged 78±14
min-1 and stroke volume 74±18 ml. The systolic and diastolic aortic pressures were on average 144.3/80.2
mmHg, respectively, with a mean of 107.8 mmHg. The pulmonary artery wedge pressures were all normal or slightly low at 8.4±3.8 mmHg. The pulmonary vascular resistance (PVR) averaged 3.5±1.5
mmHg·l-1·min-1·m-2 BSA. Elevated PVR (>3.5 units) was found in 6 out of 11 patients. The systolic pulmonary artery pressure was 30.4±8.9
mmHg. Seven out of 11 had pressures above

Calculations and statistics

The calculations involved have been reviewed earlier by ANGOU-LINDSKOG et al. [20]. Means, standard deviations, standard errors of the mean were computed according to standard equations. The statistical differences were determined using Student’s t-test for paired observations. p<0.05 was considered significant.

Results

Work capacity. Symptom limited work capacity, Wsl, was determined in 8 out of 11 patients and was on average 111 Watts. Maximum heart rate and maximum rate of breathing averaged 152 min-1 and 40.3 min-1, respectively. The reason for interrupting the test was severe dyspnoea in all patients. Patients 1, 5 and 11, who all had low TLco and small lung volumes, also had low Wsl (table 1).

Lung volumes. FRC was on average 65.1%, of predicted. Vital capacity (VC) and total lung capacity (TLC) averaged 64.8 and 68.0% respectively. Patients 1, 5 and 11 all had small TLC.

Dynamic spirometry. Forced expiratory volume in one second (FEV1) was markedly reduced to an average of 59.2±23% of predicted. Only patient 9 had a normal value. Forced expiratory volume (FEV1) percentage was 92.4±23% of predicted. Patients 1, 2, 3, 6, 7 and 11 had markedly reduced values. These patients had flow-
V/Q IN SARCOIDOSIS

30 mmHg. One patient (No. 11) had a severe pulmonary hypertension (97 mmHg). Elevated right atrial pressure (7 mmHg) was found in 2 out of 11 patients.

Central haemodynamics during exercise. The work load used was mild, increasing oxygen uptake to an average of 665 ml STPD·min⁻¹. Increase in cardiac output was normal in relation to oxygen uptake. Heart rate rose to 106 min⁻¹ and stroke volume remained unchanged. Arterial mean pressure increased normally. Pulmonary wedge pressure remained normal but pulmonary resistance increased significantly to 5.2 mmHg·l⁻¹·min⁻¹·m⁻² BSA resulting in a significant rise in pulmonary arterial mean pressure. Patient 11 could only be studied at rest because of the severity of the disease.

V/Q and gas exchange at rest (tables 2 and 3). The patients were slightly sedated and relaxed. The oxygen uptake was 18.2 % of predicted and the respiratory quotient (RQ) was 0.80. Total ventilation was normal with a moderate tachypnoea of 15.5 min⁻¹. Tidal volume averaged 0.55 l BTPS min⁻¹. Alveolar ventilation was normal with a normal arterial carbon dioxide tension ($\text{Paco}_2$). The Bohr dead space calculated from measured $\text{Paco}_2$ was 0.22 ml BTPS and $\text{Vd/Vt}=0.42$. Measured arterial oxygen tension ($\text{Pao}_2$) was low and the measured alveolar-arterial $\text{O}_2$ difference was elevated, 4.2 kPa on average. The total venous admixture was 8.9% of cardiac output. Patients 1, 5 and 11 all had high venous admixture, mean 15%. The distributions of ventilation and perfusion in relation to log V/Q for the whole group are illustrated in figures 3 and 4 and presented in numerical values in table 3. There was a small shunt in all patients averaging 1.0%. Three out of 11 had slight perfusion of regions with low V/Q (0.005–0.1) and one patient (No. 11) perfused this region with 9.3% of cardiac output. There was an increase in wasted ventilation calculated from the ventilation distribution (wasted ventilation equal to the sum of fractional ventilation of regions with V/Q between 10–100). The perfusion distribution had a low mean value 0.69 with a large (twice normal) log sd [24]. The ventilation distribution was centred around a mean value of 1.15 also with a larger than normal dispersion. Calculated $\text{Pao}_2$ was slightly but
significantly higher than measured. Calculated \( P_{aco2} \) agreed well with the measured one. Calculated \( \alpha-a)_{a2} \) difference was significantly smaller than the measured one. In patients 1, 5 and 11 calculated \( \alpha-a)_{a2} \) difference was larger (7.0 kPa) than the calculated one (4.5 kPa).

### Table 2.
Physiological variables at rest and during mild exercise in sarcoid patients \((n=11)\) with pulmonary involvement

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Rest</th>
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<th>Patient No. 11</th>
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<td>( \text{VO}_2 )</td>
<td>ml STPD·min(^{-1})</td>
<td>257±42</td>
<td>665±145</td>
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| \( \text{a-v})_{o2} \) | ml \(
| \( \text{Q} \) | Fick | 5.7±1.2 | 8.3±2.1 | 2.7 |
| \( \text{HR} \) | min\(^{-1}\) | 78±14 | 106±13 | 95 |
| \( \text{SV} \) | ml | 74±18 | 78±16 | 28 |
| \( \text{VA} \) | \text{ml} \text{BTPS}·min\(^{-1}\) | 8.2±1.9 | 21.6±6.8 | 11.0 |
| \( \text{f} \) | | 15.5±4.3 | 25.6±7.4 | - |
| \( \text{VT} \) | | 0.5±0.13 | 0.87±0.38 | 0.42 |
| \( \text{V0 Bohr} \) | | 0.22±0.005 | 0.33±0.13 | 0.27 |
| \( \text{PPA} \) | mmHg | 19±5 | 36±12 | 60 |
| \( \text{Pw} \) | mmHg | 8±4 | 13±11 | 6 |
| \( \text{PVR} \) | units | 108±17 | 126±22 | 82 |
| \( \text{Pao}_{2m} \) | kPa | 9.7±1.3 | 9.1±2.0 | 5.7 |
| \( \text{Paco}_{2m} \) | kPa | 10.3±1.2 | 10.51±1.6 | 8.4 |
| \( \text{Paco}_{2t} \) | kPa | 5.1±0.4 | 5.1±0.5 | 4.5 |
| \( \text{Pao}_{2e} \) | kPa | 5.2±0.4 | 5.2±0.7 | 4.5 |
| \( \text{QVA/QT} \) | % | 8.9±4.0 | 5.4±3.4 | 17.9 |
| \( \text{Qus/Q} \) | % | 1.0±0.8 | 0.7±0.6 | 1.7 |
| \( \text{P}(\alpha-a)_{o2m} \) | kPa | 4.1±1.3 | 5.1±2.4 | 8.9 |
| \( \text{P}(\alpha-a)_{o2e} \) | kPa | 2.7±0.8 | 2.5±1.2 | 6.3 |
| \( \text{Vd}/\text{VT} \) | Bohr | 0.42±0.11 | 0.39±0.12 | 0.63 |
| \( \text{AP}_{02} \) | kPa | 0.2±0.2 | | |

\( \text{VO}_2 \): Oxygen uptake; \( \text{a-v})_{o2} \): arteriovenous oxygen difference; \( \text{Q} \) Fick: cardiac output; \( \text{f} \): heart rate; \( \text{SV} \): stroke volume; \( \text{VA} \): minute ventilation; \( \text{f} \): respiratory rate; \( \text{VT} \): tidal volume; \( \text{V0 Bohr} \): physiological deadspace; \( \text{PPA} \): pulmonary arterial mean pressure; \( \text{Pw} \): pulmonary wedge mean pressure; \( \text{PVR} \): pulmonary vascular resistance; \( \text{P}_{o2} \): systemic mean arterial pressure; \( \text{Pao}_{2m} \): measured \((m)\) and calculated \((c)\) arterial oxygen partial pressure; \( \text{Paco}_{2m} \): measured \((m)\) and calculated \((c)\) arterial carbon dioxide pressure; \( \text{QVA/QT} \): venous admixture; \( \text{Qus/Q} \): rel. shunt flow; \( \text{P}(\alpha-a)_{o2m} \): measured \((m)\) and calculated \((c)\) alveolo-arterial oxygen pressure difference, \( \text{Vd}/\text{VT} \) Bohr dead space to tidal volume ratio; \( \text{AP}_{02} \): deviation of oxygen partial pressure at an arterial oxygen saturation of 50%, deviation of measured from normal \( \text{P}_{02} \) (26.6) kPa.

### Table 3.

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<td>0.005-0.1</td>
<td>0.6±1.2</td>
<td>9.5</td>
</tr>
<tr>
<td>0.1-10</td>
<td>98.2±1.2</td>
<td>87.9</td>
</tr>
<tr>
<td>10-100</td>
<td>0.2±0.3</td>
<td>1.1</td>
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<tr>
<td>&gt;100</td>
<td>0</td>
<td>0</td>
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\( \text{V}/\text{Q} \): Oxygen uptake; \( \text{Q}/\text{Q}\) x 100: arteriovenous oxygen difference; \( \text{Y}/\text{V}\) x 100: mean \( \text{V}/\text{Q} \) for the distributions of perfusion and ventilation and mean values for the log standard deviation of these distributions. All eleven patients had pulmonary sarcoidosis. Data on one subject is given separately in this table.
V/Q IN SARCOIDOSIS

$0.8$ $0.6$ $0.4$ $0.2$ $0$ $10^{-2}$ $10^{-1}$ $1$ $10$ $100$ Log ventilation-perfusion ratio

Fig. 3. - Perfusion, $\text{min}^{-1}$, and ventilation, $\text{min}^{-1}$, in relation to log V/Q using a 50 compartment model in patient 10 with sarcoidosis of the lungs type III with severe roentgenological changes. Note the almost normal main modes, small shunt and large dead space to tidal volume ratio ($V_{D}/VT$) $\bigcirc$ $Q_{I}$ $\bigcirc$ $Q_{A}$ $\bigcirc$ $Q_{T}$.

$V/Q$ and gas exchange during exercise. The work load used was low, increasing oxygen uptake to an average of 665 ml min$^{-1}$. Respiratory rate increased to 25.6 min$^{-1}$. RQ remained low in all patients. One patient (No. 9) had slight alveolar hypventilation with a $P_{a}CO_2$ of 6.2 kPa. The others had normal alveolar ventilation with a $P_{a}CO_2$ of 5.1 kPa. Bohr dead space calculated from measured $P_{a}CO_2$ remained unchanged, $V_{D}/VT$ 0.39. Measured $P_{a}O_2$ was slightly reduced to 9.1 kPa and the measured $P(A-a)O_2$ increased to 5.1 kPa. Total venous admixture decreased to 5.4% ($p<0.05$) of cardiac output. In patients 1 and 5 the $P(A-a)O_2$ measured was 5.6 and 9.3 kPa while that calculated amounted to 2.4 and 4.4 kPa. Mean values for both ventilation and perfusion distributions were shifted towards higher V/Q values still with larger than normal log SD. The shunt disappeared in three patients and remained unchanged in the others. Only two patients had significant perfusion of regions with low V/Q. There was a slight reduction of wasted ventilation determined with the inert gas technique and of perfusion of regions with V/Q between 0.1-1.0. The calculated $P_{a}O_2$ remained unchanged while the measured $P_{a}O_2$ was 0.4 kPa lower ($p<0.05$). Measured and calculated $P_{a}CO_2$ agreed well.

Fig. 4. - Relative perfusion, $Q/Q_T$, (left) and ventilation, $V/V_T$, (right) in relation to log ventilation-perfusion ($VA/Q$) in a 50 compartment model in patients with sarcoidosis of the lungs. Eleven patients were studied at rest and 10 during mild exercise. Note the presence of a small shunt, small perfusion of regions with low V/Q in 4 out of 11 patients (black areas) and ventilation and perfusions with regions of high V/Q in 5 out of 11. During mild exercise the distributions look less heterogenous.
ACE activity (table 1) did not correlate significantly with any of the observed deviations from normality in the studied lung function tests.

Discussion

The patients studied in the present investigation had endobronchial biopsy-proven sarcoidosis of roentgenological types II and III. Their symptom limited work capacity was markedly reduced as were the lung volumes and single breath transfer factor for carbon dioxide.

Flow-volume curves indicated the presence of obstructive lung disease and the pulmonary vascular resistance was elevated in most of the patients at rest and increased to abnormal values during slight exercise, indicating significant vascular obstruction and/or destruction. Thus there were indications of airway as well as vascular involvement.

Perfusion scintigrams revealed abnormalities in all patients and radiospirometry showed a slower than normal turnover of gas. Furthermore, the distributions of ventilation and perfusion on V/Q showed a small shunt in all patients and a small perfusion of regions with low V/Q in some patients. Other patients had ventilation and perfusion of regions of high V/Q. Mild exercise tended to reduce these abnormalities. The combined effect of these deviations was a slightly lowered Pao₂ and moderately elevated P(\(\Delta_a\)O₂). There were thus indications of restrictive and obstructive airway disease as well as vascular disturbances. The influence on alveolar gas exchange was, however, only slight under the conditions studied. This implies, as is also indicated by the radiospirometry and inert gas studies, that the matching of ventilation and perfusion was to a large extent adequate at rest and during mild exercise.

The quality of determinations of distributions of ventilation and perfusion in relation to V/Q with the inert gas technique is related to the validity and reproducibility of the inert gas analyses and to the achievement of steady state conditions during measurements. The compatibility between data obtained for retention and excretion and the derived distribution can be evaluated from the residual sum of squares (RSS) in the least squares analysis used. In the present study, all measurements had values for RSS below 10 which is considered acceptable [19].

WAGNER et al. [25] and JERNHUND-WILHELMSSON et al. [26] found no significant differences between measured and calculated Pao₂ at rest in patients with interstitial lung disease. In the present study a difference was present and this difference was greater in patients with the lowest Pao₂ (fig. 5). During mild exercise, measured P(\(\Delta_a\)O₂) increased slightly but not significantly, while the calculated value remained unchanged which is in agreement with earlier observations [26]. The slope of the regression of calculated to measured Pao₂ was significantly less than one and the difference between calculated and measured Pao₂ increased with low Pao₂ (fig. 5).

Fig. 5. Calculated arterial oxygen tension (Pao₂) in relation to measured (Pao₂) at rest and during steady state supine exercise in 10 patients with lung sarcoidosis. The regression line for values at rest is $y = 0.84x + 2.1$, $r = 0.93$ and during exercise $y = 0.62x + 5.0$, $r = 0.78$. The figure illustrates the presence of a diffusion limitation during exercise in patients with Pao₂ < 8 kPa.

Fig. 6. Calculated (Pao₂-m) minus measured arterial oxygen tension in relation to single breath transfer factor of the lungs in as percentage of predicted, Tlco%, in eleven patients with lung sarcoidosis studied at rest, (open circles), and during mild exercise, (filled circles). The regression line at rest was $y = 1.16 - 0.08x$, $r = 0.55$ and during exercise $y = 3.14 - 0.24X$, $r = 0.69$. There is a significant correlation both at rest and during exercise which also indicates the presence of a diffusion limitation both at rest and during exercise.
These observations indicate the presence of diffusion limitation of oxygen transport even at rest and at the low values for oxygen uptake studied. Further support for this is found in the significant correlation (fig. 6) between the differences in calculated and measured \( P_{aO_2} \) and \( TLCO \) (absolute values or as percentage of predicted). WAGNER et al. [25] found no regions with \( V/Q \) values above the upper limit of normal. In the present studies five patients at rest had modes above the normal variation. This is in agreement with JERNUDD-WILHELMSSON et al. [26] and indicates disturbances in the perfusion of the lung. In the present patients these modes disappeared during mild exercise probably indicating a more homogeneous perfusion of the lung.

Tomographic analysis of perfusion scintigrams in an ongoing study (Holmgren, manuscript in preparation) on patients with interstitial lung disease, have shown that at rest in the supine position there is often a significant redistribution of the blood flow to the dependent parts of the lungs. This can explain the presence of ventilation in regions of high \( V/Q \) and also the disappearance of these modes during exercise when the lung is more evenly perfused.

It can be concluded that in a group of patients with pulmonary sarcoidosis types II and III with indications of restrictive as well as obstructive lung disturbances, increased pulmonary vascular resistance and reduced transfer factor, only a moderate degree of mismatch of ventilation and perfusion at rest and during mild supine exercise was present. The difference between calculated and observed values indicates diffusion limitation even at the low levels of oxygen transport studied. In one patient with severe pulmonary hypertension and marked arterial hypoxaemia, having a pronounced venous admixture at rest and an extremely reduced diffusing capacity, the difference between calculated and observed \( P_{aO_2} \) probably indicates that a marked diffusion limitation is present already at rest.

References

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\( V/Q \) et échanges gazeux alvéolaires dans la sarcoidose pulmonaire. A. Eklund, L. Bromann, M. Bromann, A. Holmgren. RÉSUMÉ: Onze patients atteints d'une sarcoidose pulmonaire de type II ou III ont été examinés en ce qui concerne la distribution régionale de la ventilation et de la perfusion, les échanges gazeux alvéolaires et les limites de diffusion au repos et à l'effort. Tous avaient une réduction de la capacité de travail due à une dyspnée. Les volumes étaient diminués à
50-65% des valeurs normales. Les courbes débits-volumes indiquaient des modifications du type obstructif. Le facteur de transfert était réduit à 75% des valeurs prédites (extrêmes: 16-120%). La scintigraphie de perfusion démontre des défauts marqués chez 7 patients sur 11. La radio-spirométrie montre, dans l’ensemble, des troubles de la congruence de la ventilation et de la perfusion, et une prolongation du "wash out" du xénon. On note une admission veineuse au repos atteignant 8.9%. La PaO₂ artérielle atteint 9.7 kPa. Les analyses de V/Q indiquent la présence d’un petit shunt de 1%, une perfusion de régions à bas rapport V/Q chez 4 patients sur 11, une ventilation de régions avec un rapport V/Q élevé chez 5 patients sur 11, et une augmentation de la ventilation inefficace. La PaO₂ mesurée au repos était inférieure de 0.6 kPa à la valeur prédite à partir de la distribution V/Q au repos. Au cours d’exercices légers en position déclive, provoquant une dyspnée significative, la résistance vasculaire pulmonaire s’élève à des valeurs anormales (5.2 mmHg·l⁻¹·min⁻¹·m⁻² BSA). L’admission veineuse diminue à 5.4%. Le shunt reste inchangé, comme la perfusion de régions à bas rapport V/Q. La ventilation anormale de régions avec un rapport V/Q élevé, observée au repos, disparaît. Les PaO₂ mesurées diminuent à 9.1 kPa, alors que les PaO₂ calculées restent inchangées. Donc, la P(A-a)O₂ au repos (4.2 kPa) était due pour 70% au shunt et au marque de congruence V/Q. Au cours de l’effort, la P(A-a)O₂, mesurée augmente davantage, jusqu'à 5.1 kPa, tandis que la valeur calculée de P(A-a)O₂ reste inchangée et n’est causée que pour 50% par les shunts et les troubles V/Q. La régression des différences observées entre les valeurs calculées et mesurées de PaO₂ sur TLCO, indique une limitation significative de la diffusion, à la fois au repos et au cours de l’effort léger. 

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