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Heterogeneous ventilation and perfusion: a sensitive indicator of lung impairment in nonsmoking coal miners

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Heterogeneous ventilation and perfusion: a sensitive indicator of lung impairment in nonsmoking coal miners. H. Susskind, J.C. Acevedo, J. Iwai, D.L. Rasmussen, D.K. Heydinger, H.R. Pate, W.H. Harold, A.B. Brill.
ABSTRACT: Twenty life-long nonsmoking West Virginia coal-miners participated in a study to amplify the role of focal irregularities on regional ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) and to develop an improved method for the early detection of coal-workers' pneumoconiosis. Their mean age was 59.3 yr and they averaged 35.2 years' exposure to coal dust. Conventional pulmonary function tests were supplemented by measurement of $\dot{V}$, $\dot{Q}$ and lung volume (V), using radioactive Kr-81m, Tc-99m MAA and Xe-127, respectively, to determine regional abnormalities in lung function. A computer analysis of the regional distributions of $\dot{V}/V$, $\dot{Q}/V$ and $\dot{V}/\dot{Q}$ was performed, and their topographical distributions and indices of heterogeneity (HI) computed. $\dot{V}/V$ and $\dot{Q}/V$ were significantly reduced in the lower third, and increased in the upper two-thirds of the miners' lungs; $\dot{V}/\dot{Q}$ was reduced in the upper half. The miners' $\dot{V}/V$ and $\dot{Q}/V$ were more heterogeneous ($p < 0.001$) than that of eleven age-matched controls, with mean ventilation HI values of 0.190 ± 0.027 and 0.133 ± 0.011, respectively, and mean perfusion HI values of 0.206 ± 0.022 and 0.164 ± 0.041, respectively. $P(A-a)O_2$ correlated positively ($r = 0.72$; $p < 0.001$) with ventilation HI. Gas exchange was the most significant functional measurement, being abnormal in 19/20 subjects. In contrast, conventional spirometric measurements were within the predicted normal limits in all but four miners.
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Simple coal-workers' pneumoconiosis (CWP) in its early stages is not generally associated with overt symptoms or other detectable physical signs, so that there may be no early warning [5]. Even chest radiographs, which provide the principal basis for the diagnosis of CWP, do not show changes in the lungs until the disease is well established, or after complications, such as emphysema or chronic bronchitis, have occurred. In many patients, chest radiographs remain normal. The earliest pathological changes occur in the alveoli and respiratory bronchioles, the gas exchange regions of the lung, which makes resulting early ventilatory changes in lung function extraordinarily difficult to detect [26]. Thus, pulmonary function screening tests routinely used to measure ventilatory capacity and other spirometric parameters are not usually helpful in diagnosing the early stages of simple CWP [26]. Sophisticated measurements of lung mechanics revealed little alteration except for some hyperinflation, occasional slight loss of lung recoil pressure, and sometimes obstruction within peripheral airways [26]. On the other hand, abnormalities of pulmonary gas exchange consisting of slight increases in $P(A-a)O_2$, and mild hyperventilation on exercise, were found in simple CWP, even in the absence of impaired ventilatory function [11, 14, 15, 31]. Tests that measure the distribution of ventilation ($\dot{V}$), such as the ratio of closing capacity to total lung capacity (TLC) and the ratio of dynamic to static compliance, were also successful in detecting lung impairment. These results indicate the presence of regional lung abnormalities in simple CWP, which cannot be evaluated properly with studies of overall pulmonary function. It is therefore surprising that only a few studies of coal miners have utilized radioisotopes [25, 32, 34, 38, 39], because radioactive tracers provide the only means to both measure regional $\dot{V}$ and pulmonary perfusion ($\dot{Q}$) and determine their precise location in the lungs. The development of other objective criteria would thus be of great help in evaluating pulmonary impairment related to coal dust exposure.

A comprehensive study was therefore conducted jointly by Brookhaven National Lahoratory (BNL) and Marshall University School of Medicine (MU) to: 1) amplify the role of focal irregularities on regional $\dot{V}$ and $\dot{Q}$ of nonsmoking coal miners and 2) develop a very sensitive objective method to quantitate pulmon-

ary function impairment. Two approaches were followed involving the measurement of, and comparison with, a healthy control group of: 1) apex-to-base topographical distributions of ventilation per unit volume ($\dot{V}/V$), perfusion per unit volume ($\dot{Q}/V$), and the $\dot{V}/\dot{Q}$ ratio in each lung and 2) a texture analysis, commonly used in image processing, of the regional distributions of $\dot{V}$ and $\dot{Q}$ to provide an index (HI) (See Computer analysis section) indicating their degree of heterogeneity and then correlating the ventilation HI with a measured overall gas exchange parameter.

Subjects and methods

Two working and eighteen retired male West Virginia coal miners, who were life-long nonsmokers, participated in this study. They were selected by physicians at MU on the basis of long working exposure to coal dust with minimal ventilatory obstruction and radiographic changes, but with dyspnoea and other complaints. Nine additional miners with cardiac problems, chest trauma and obesity were eliminated from the study. The age-matched control group consisted of eleven healthy BNL volunteers (nine males and two females) with a mean age of 54.2 ± 8.4 yr (range: 45–71 yr). Their characteristics are shown in table 1. All were life-long nonsmokers and included blue collar and laboratory workers, whose pulmonary function results and ventilation-perfusion studies were within normal limits. Except for measurement of compliance, the same studies were carried out for both miners and controls. The miners underwent a comprehensive series of studies to assess their medical, physiological and biochemical status during a five-day stay at the Hospital of the Medical Research Center at BNL. These studies included a medical history and physical examination, laboratory analyses of blood, urine, stools and sputum, electrocardiogram, chest roentgenogram, complete pulmonary function workup and nuclear medicine studies with radioactive tracers to measure regional $\dot{V}$, $\dot{Q}$ and V. The subjects were seated upright for all measurements.

Each subject was interviewed by a physician and answered a detailed series of questions concerning respiratory symptoms, smoking and occupational exposure history, and demographic information. The questionnaire was modified from that of the Medical Research Council of Great Britain. Posteroanterior and right lateral chest radiographs were interpreted by a NIOSH-certified B reader, using the 1980 ILO Classification system and standard radiographs. Sputum production was evaluated both on the basis of the questionnaire and 24 h collections during the patient's stay at the hospital. Average sputum collections of <0.25 ml per day were considered to be unproductive, between 0.25 and 2.35 ml per day productive, and >2.35 ml per day highly productive. The grade of dyspnoea was determined from the questionnaire, as well as by observation of the patient during his hospital stay.

Table 1. - Controls' pulmonary function and gas exchange measurements

	Percent of predicted values	
	$\bar{x} \pm$ SD	Range
Age* yr	54.2± 8.4	45–71
Vital capacity *l*	105.6±13.9	84.6–125.0
Residual volume *l*	81.1±17.4	59.3–113.9
Total lung capacity *l*	96.1±13.6	81.1–119.1
Functional residual capacity *l*	79.5±16.8	62.2–110.0
FEV_1 *l*	103.4±11.9	82.5–121.5
FEV_1/FVC* %	79.6± 4.3	70.0–84.9
Maximum forced expiratory flow rate $l \cdot s^{-1}$	120.6±20.2	88.4–153.0
Maximum midexpiratory flow rate $l \cdot s^{-1}$	100.7±18.8	73.0–125.7
Maximum forced expiratory flow rate at 50% VC $l \cdot s^{-1}$	84.6±24.9	56.6–127.2
Maximum forced expiratory flow rate at 75% VC $l \cdot s^{-1}$	83.0±24.2	55.5–110.8
Closing volume/vital capacity %	95.9±15.1	68.7–116.1
Pa_{O_2}* mmHg	96±7	85–104
Pa_{CO_2}* mmHg	36±3	35–40
$P_{(A-a)O_2}$* mmHg	13±6	4–20
DLCO $ml \cdot min^{-1} \cdot mmHg^{-1}$	127±18	97–148
HI*		
Ventilation	0.133±0.011	0.109–0.149
Perfusion	0.164±0.041	0.103–0.232

*Actual measured values

Lung volumes, maximal expiratory flow-volume loops, maximum ventilatory volume (MVV) and closing volume (CV_f/VC) were measured with a 12 *l* dry-seal spirometer (CPI model 220), according to standard techniques [20]. Functional residual capacity (FRC) and residual volume (RV) were determined by the helium dilution technique. Values of vital capacity (VC) and TLC below 80%, and of RV and FRC greater than 120% of predicted were considered abnormal. Values of forced expiratory volume in one second (FEV_1) below 75% of predicted and FEV_1/FVC (forced vital capacity) below 70% were considered abnormal. Closing volume was determined by the bolus technique, using 5 ml boluses of helium [36]. Thoracic gas volume (Vtg) and airway resistance (Raw) were measured in a body plethysmo-

graph (CPI model 2000 TB). Values of Raw in excess of 5 $cmH_2O \cdot l^{-1} \cdot s$ were considered abnormal. Both static and dynamic compliances were measured using an oesophageal balloon to determine pleural pressure. Values of static compliance greater than 400 and less than 100 $ml \cdot cmH_2O^{-1}$ were considered abnormal.

Blood samples were drawn and immediately analysed in duplicate in a blood gas analyser (Radiometer model PHM 72) for arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}) and pH; bicarbonate (HCO_3^-), base excess, and O_2 saturation were also calculated. Minute volume and alveolar ventilation, tidal volume (V_T), respiratory rate, oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), physiological and anatomical dead space (V_D), physiological and anatomical V_D/V_T and O_2 and CO_2 ventilatory equivalents were measured with the Metabolic Measurement Cart (Beckman Instruments). The instrument was calibrated for each study. The steady-state values at the time of blood sampling were used for data analysis. Alveolar-arterial pressure difference for oxygen ($P(A-a)_{O_2}$) was considered abnormal if it exceeded the predicted value by 2 SD.

Diffusing capacity (DLCO) was measured by the end-tidal carbon monoxide (CO) steady-state method [7], with a 0.1% CO-air mixture, and using a CO Analyser (Morgan model 014), a CPI spirometer (model 220) and an automated apparatus to control gas flows (Medicraft model M-810). Values less than 80% or greater than 140% of predicted were considered abnormal.

Predicted values for lung volumes were obtained from GOLDMAN and BECKLAKE [16]; FRC from BOREN *et al.* [10]; FEV_1 from KORY *et al.* [21]; maximal forced expiratory flow (FEF_{max}) from LEINER *et al.* [22]; forced mid-expiratory flow ($FEF_{25-75\%}$) from MORRIS *et al.* [29]; FEF when 50% of FVC has been exhaled ($FEF_{50\%}$) from CHERNIACK and RABER [12]; $FEF_{75\%}$ from BASS [6]; CV/VC from SUSSKIND *et al.* [36]; Pa_{O_2}, $P(A-a)_{O_2}$ and Pa_{CO_2} from MELLEMGAARD [24]; and steady-state DLCO from BATES *et al.* [8].

Radionuclide imaging of regional lung perfusion, ventilatian and volume

Regional pulmonary blood flow and regional ventilation were measured with 4 mCi Tc-99m labelled albumin macroaggregates (MAA) injected intravenously and during continuous inhalation of the short-lived Kr-81m gas ($t_{\frac{1}{2}} = 13$ s), respectively. In addition, regional lung volume was measured following the inhalation and equilibration of 5 mCi Xe-127 gas. The procedure was described previously [17].

The regional Kr-81m count rate for normal respiratory rates is determined largely by the inflow of fresh amounts of Kr-81m, *i.e.* regional ventilation [2]. Excellent images of regional ventilation can be obtained using Kr-81m with any desired number of total counts and correspondingly good counting statistics. However, the theory is very complex, so that quantitating the Kr-81m count distributions in terms of absolute $\dot{V}/V$ ratios is difficult. During steady-state inhalation of Kr-81m, the amount of tracer present in any lung region remains constant with time. Under these conditions, the rate of arrival of Kr-81m in a lung region must be equal to its rate of removal. Thus, the amount of Kr-81m present in any lung region is determined by a balance between its rate of arrival in the inspired breath and its rate of removal by ventilatory washout and radioactive decay. So long as radioactive decay (Kr-81m decay constant = 3.2 per min) dominates the removal process, regional count rates during steady-state inhalation of Kr-81m at normal respiratory rates reflect primarily inspired ventilation of that region. In obstructed regions with poor inspired ventilation, the effect of radioactive decay will be proportionately greater and the Kr-81m count rate will be lower. Thus, poorly ventilated lung regions are shown on the image collected during steady-state inhalation of Kr-81m as less dense areas. However, the relationship between Kr-81m count rate in the lung and ventilation becomes nonlinear at higher turnover ratios, above a theoretical limit of $2.5\ l \cdot min^{-1} \cdot l^{-1}$ [3], as the ventilatory washout process overrides radioactive decay. This results in equilibration between inspired and alveolar concentrations of Kr-81m, and regional count rates will merely reflect regional lung volume, with a corresponding tendency to underestimate $\dot{V}$. The theory and its limitations and approaches to quantitation of Kr-81m results have been extensively discussed by AMIS *et al.* [1] and AMIS and JONES [2].

AMIS *et al.* [1] suggested the use of an additional gas, radioactive Kr-85m, which has a longer half-life than Kr-81m, as a marker of lung volume after equilibration. Its use also permits the ventilatory turnover of the entire lung to be estimated from the first minute of Kr-85m washout from the total lung field, from which regional $\dot{V}/V$ in absolute units could be obtained. In our study, long-lived Xe-127 ($t_{\frac{1}{2}} = 36.4$ d), instead of Kr-85m, was inhaled as the volume marker. The physical characteristics of Xe-127 for imaging purposes are more advantageous than those of Kr-85m, and the photon energies are much closer to those of Kr-81m. However, we did not use the total lung clearance rates of Xe-127 in our data analysis. Instead, our results of regional $\dot{V}/V$ were calculated from the ratio of the count rates obtained with Kr-81m to those of Xe-127 in each pixel, and expressed in arbitrary units. Inasmuch as the maximum $\dot{V}/V$ ratio for any individual lung slice exceeded 2.5 in only four instances in one subject, all the others being less than 2.0, we feel that the subjects' values of $\dot{V}/V$ properly reflect the relative distributions in their lungs.

The use of Xe-127, produced by the Brookhaven Linac Isotope Producer (BLIP), has overcome the major limitations of Xe-133, commonly used for ventilation studies [4, 13]. Its three photons have a higher energy (172, 203 and 375 keV) and abundance (25, 68 and 18%, respectively) than the 81-keV

photon energy (37% abundance) of Xe-133. This provides better intrinsic spatial resolution and higher counting rates. In addition, the Xe-127 has better chest wall and lung tissue penetration with less photon scattering than Xe-133.

A large field-of-view scintillation camera (Ohio-Nuclear Inc. Series 110) was used in all studies. To minimize the possibility of patient movement between measurements, the same 280-keV medium-resolution collimator was used for both Kr-81m and Tc-99m. Twenty-five and 15% windows were centered over the 140-keV Tc-99m and 190-keV Kr-81m peaks, respectively. A 400-keV high-energy collimator was used for Xe-127 with a 20% window encompassing both the 172- and 203-keV photon peaks. The 400-keV collimator was used to prevent septal penetration by the 375-keV photons [4].

Care was taken to position the subjects in front of the camera for the Tc-99m/Kr-81m and then the Xe-127 studies. The Tc-99m images were used to centre both lungs in the camera field, whilst the subject was seated in front of the scintillation camera. In the posterior position, three spots were marked on the subject's chest and aligned with an optical grid projected on the camera face. These were subsequently used to position the subject for the Xe-127 study.

Five hundred thousand count scintiphotos of the Kr-81m images were obtained in the posterior, anterior, and right and left posterior oblique positions, and were interdigitated with Tc-99m images, using a computer (Digital Equipment Corp. PDP 11/34 Gamma 11 system) and storing the data for each $\dot{V}$ and $\dot{Q}$ image on magnetic tape. Xe-127 scintiphotos were obtained at TLC during the first deep inspiration and again after equilibration. Then continuous 1 min scintiphotos were obtained during tidal breathing sequentially at equilibrium and during the subsequent washout of radioxenon. Computer acquisition at 5 s intervals was carried out during the entire study. The four Tc-99m MAA and Kr-81m images were then compared with Xe-127 images in the posterior position obtained from the inspiration of the initial tracer bolus during a 30 s breath-hold, after equilibration, and for the first 5 min of washout.

Computer analysis

The radioisotope distributions for each subject were analysed with a computer (Digital Equipment Corp., VAX 11/780 system) and displayed in a 64×64 matrix with a grey scale. After 2-point smoothing of the posterior Kr-81m, Tc-99m and 1 min Xe-127 equilibrium images, the contours of the lung fields were determined automatically, by setting all pixels below a 20% threshold to zero. However, within the lung fields all values were included. All images were then normalized to 500,000 counts. In order to locate lung regions with impaired $\dot{V}$ and $\dot{Q}$, the lungs were divided into a series of 6.5×6.5 mm square areas (pixels), each representing activity in the underlying lung tissue. This size was determined from tracer measurements of full-width-at-half-maximum to measure image resolution. The activities of Tc-99m, Kr-81m, and Xe-127 in each pixel were then calculated by computer and printed. In addition, the Kr-81m and Tc-99m activities in each pixel were divided by the corresponding Xe-127 activity to correct each one for lung volume. The results for each pixel were thus approximately proportional to $\dot{V}/V$ and $\dot{Q}/V$, respectively. The mean $\dot{V}/V$ and $\dot{Q}/V$ values and dispersions, as well as that of the $\dot{V}/\dot{Q}$ ratio, were measured for 6.5 mm-thick horizontal lung slices, and individual slice-by-slice distributions between apex and base in each lung were computed. The results were plotted as a function of lung-slice position between apex and base (fig. 1).

Since simple CWP is manifested by the relatively small, but widespread distribution of focal damage, and the local distributions of $\dot{V}/V$ and $\dot{Q}/V$ were found to be irregular, both horizontally and vertically, the degree of this heterogeneity was used as an index (HI). It must be stressed that these local irregularities in the horizontal as well as vertical direction are superimposed on the normal apex-to-base ventilation and perfusion gradients inherent in the upright lungs of all seated subjects. It is this additional irregularity that distinguishes the coal miners from the healthy control group by increasing HI. It was determined as follows: 1) the value of $\dot{V}/V$ or $\dot{Q}/V$ was computed for each pixel; 2) the average of the differences between the values of $\dot{V}/V$ and $\dot{Q}/V$ for each pixel and those of their four nearest-neighbour pixels was computed; 3) the overall mean value of these average individual nearest-neighbour differences for all the pixels was then calculated and constitutes an index (HI) indicating the degree of $\dot{V}$ or $\dot{Q}$ heterogeneity.

Statistical analysis

Correlations were obtained from a least-square fit of the data, calculated by linear regression analysis. Their statistical significance was determined by applying Student's t-test. The statistical significance of the difference between means of the miners and controls was determined by applying the unpaired t-test.

Results

The mean age of the twenty miners was 59.3 ± 5.8 yr (range: 43–66 yr), and they were exposed to coal dust for an average of 35.2 ± 6.4 yr (range: 26–45 yr) (table 2). However, no accurate data regarding actual environmental exposure are available. They were retired for a mean of 3.0 yr (range: 0 ± 8 yr) at the time of the study. All miners presented with complaints of dyspnoea; additional complaints included cough, sputum production, wheezing, and chest and joint pains, but these complaints were seldom the most prominent symptoms. Ten miners had normal chest radiographs, while the remainder showed varying degrees of abnormality, ranging from p type opacities to fibrotic changes. All miners were found to

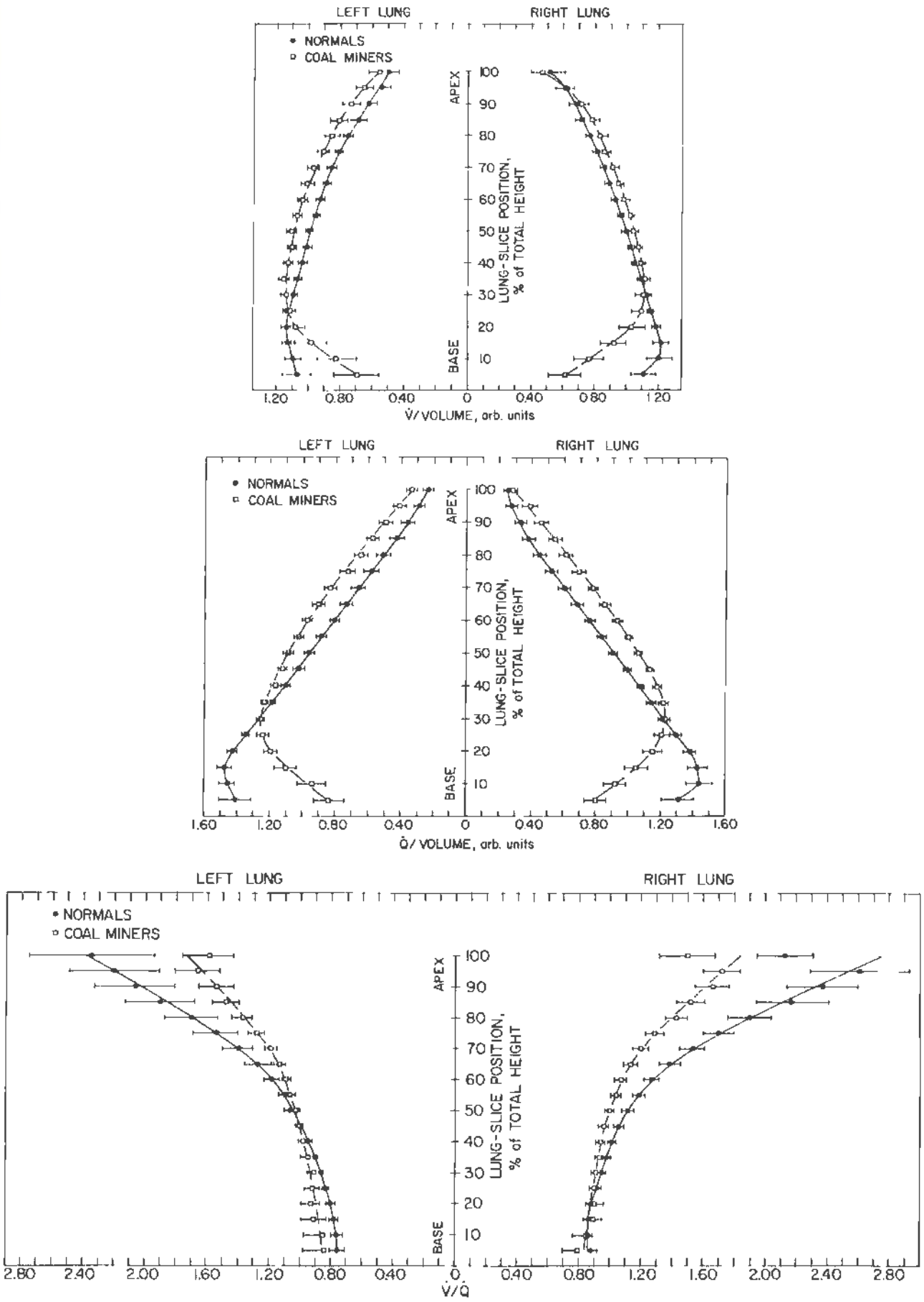

Fig. 1. Topographical distribution of $\dot{V}/V$ (upper panel), $\dot{Q}/V$ (middle panel) and $\dot{V}/\dot{Q}$ (lower panel) in arbitrary units with lung position between apex and base for healthy subjects and coal miners. Mean ± SEM.

Table 2. - Miners' characteristics

Subject	Age yr	Exposure to coal dust yr	Chest radiograph	Dyspnoea grade*	Productive cough†	Chronic bronchitis‡
1	58	39	normal	3	++	+
2	54	27	q/q 0/1	5	+	–
3	61	30	normal	4	–	–
4	63	40	p/p 0/1	2	+	–
5	64	38	normal	2	–	–
6	65	32	q/q 0/1	2	+	–
7	60	44	p/p 3/3	4	–	–
8	43	27	normal	2	++	+
9	57	32	p/p 1/1	5	–	–
10	61	26	normal	4	+	+
11	65	40	fine fibrotic changes	3	+	+
12	65	32	normal	5	+	+
13	58	35	interstitial fibrotic changes	4	+	+
14	51	30	r/r 1/1	4	+	+
15	53	35	r/r 2/2	4	+	+
16	56	26	p/p 1/1	4	+	+
17	66	45	normal	4	–	–
18	63	42	normal	2	–	–
19	59	41	normal	4	–	–
20	63	43	normal	5	–	–
$\bar{x}$±SD	59.3±5.8	35.2±6.4				

*2: short of breath walking up small hill; 3: short of breath walking on level ground with people of same age; 4: short of breath walking 1/4 mile on level ground in 15 min; 5: short of breath performing minimal physical activity; † no sputum –: <2.4 ml sputum/d +: >2.4 ml sputum/d ++; ‡ yes +: no –.

have dyspnoea on exertion, varying in severity between grades 2 and 5, as defined in table 2. Only twelve of the group had a productive cough, nine with chronic bronchitis as determined by questionnaire on the basis of cough and sputum production on most days for more than three months of the year for more than two years. The physical examination showed only minor pulmonary abnormalities.

An effort was made to correlate the miners' clinical findings with the functional measurements. However, no relationships could be found between the roentgenographic classification and sputum production, on the one hand, and spirometry, $P(A-a)O_2$, DLCO, HI and Xe-127 retention during gas washout, on the other. The degree of dyspnoea did not correlate with any of the variables.

Mean values of conventional large-airway measurements of lung function (VC, RV, TLC, FRC, FEV_1, $\%FEV_1/FVC$, MVV, FEF_{max} and Raw) were found to be similar for both miners and controls, being within normal limits in sixteen miners (table 3). One miner (No. 13) had a reduced FEV_1 (64% of predicted) and FEV_1/FVC of 69%, two (Nos 6 and 10) had FEV_1/FVC values of 68 and 69%, respectively, and the fourth (No. 9) had an elevated RV and FRC (164 and 140% of predicted, respectively). In contrast, mean values of measured small airway function were different in the two groups. One or more of the measurements were abnormal in sixteen miners (all but Nos 4, 11, 16 and 18), *i.e.* measured values of $FEF_{25-75\%}$, and of $FEF_{50\%}$ and $FEF_{75\%}$, fell below 72 and 55% of predicted values respectively, CV/VC exceeded the predicted values by 2 SD, and dynamic compliance was frequency dependent. The static compliance of one miner (No. 2) was 0.600 $l \cdot cmH_2O^{-1}$ and the dynamic compliance decreased by >20% as the respiratory frequency was increased to 60 $b \cdot min^{-1}$ in seven of the thirteen subjects measured.

The mean Pao_2 of the miners was lower than that of the controls, 86±10 *vs* 94±6 mmHg, while the mean $Paco_2$ was 34±4 mmHg for the miners (table 4) and 36±3 mmHg for the controls. At the same time, the mean $P(A-a)O_2$ of 27±12 mmHg for the miners was double that of the controls. Only four miners had Pao_2 values of 80 mmHg or less. The $P(A-a)O_2$ values of eight miners were normal, determined from MELLEMGAARD's regression equation with age [24]. Three miners (Nos 1, 6 and 15) had reduced, and four miners (Nos 10, 11, 17 and 19) had increased, steady-state DLCO values. Only one miner (No. 10) had a normal ventilation HI value (<2 SD above the mean value for the controls) (see below).

Most of the Kr-81m images showed only peripheral irregularities. Significant segmental defects were

Table 3. - Results of miners' pulmonary function measurements

	Percent of predicted values	
	$\bar{x} \pm$ SD	Range
Vital capacity *l*	108.5±11.3	87.1–129.6
Residual volume *l*	88.1±24.4	50.5–164.4
Total lung capacity *l*	100.1±11.6	81.0–133.0
Functional residual capacity *l*	86.6±17.1	69.3–140.3
FEV_1 *l*	97.4±12.2	63.7–120.5
FEV_1/FVC* %	76.5± 5.0	67.9–85.3
Maximal voluntary ventilation $l \cdot min^{-1}$	103.9±27.4	58.0–153.1
Maximum forced expiratory flow rate $l \cdot s^{-1}$	88.3±14.6	64.2–110.5
Airway resistance $cmH_2O \cdot l^{-1} \cdot s$	85.3±32.0	53.2–171.2
Maximum midexpiratory flow rate $l \cdot s^{-1}$	87.4±26.5	31.4–153.7
Maximum forced expiratory flow rate at 50% VC $l \cdot s^{-1}$	73.3±23.3	30.3–127.7
Maximum forced expiratory flow rate at 75% VC $l \cdot s^{-1}$	79.1±34.8	21.0–156.8
Closing volume/vital capacity %	124.9±24.0	77.9– steep alveolar plateau‡
Static compliance $ml \cdot cmH_2O^{-1}$	132±52	70.0–300.0
Dynamic compliance† $ml \cdot cmH_2O^{-1}$	22±19	no change –55% decrease

*Actual measured values; †percentage decrease in compliance with increase in breathing rate to 60 $b \cdot min^{-1}$;‡ no phase IV

found in only four miners. Only seven miners had minimal Xe-127 retention after 5 min of washout, two with diffuse retention and five with retention primarily in the bases. The apical regions were underperfused, primarily due to the injection of Tc-99m MAA while the miners were seated upright to match the measurement of $\dot{V}$ in this position. The $\dot{V}$ and $\dot{Q}$ images showed matching defects in 12 cases. $\dot{V}$ defects with normal $\dot{Q}$ were found in two miners, and $\dot{Q}$ defects with normal $\dot{V}$ were found in one miner. Four studies were normal.

The mean ($\pm$SEM) topographical distributions between apex and base of the twenty miners' regional $\dot{V}/V$, $\dot{Q}/V$, and $\dot{V}/\dot{Q}$ in the posterior projection were plotted in figure 1, together with the corresponding distributions for the healthy volunteers. As expected, both mean $\dot{V}/V$ and $\dot{Q}/V$ of the controls increased from apex to base, the latter with a steeper gradient. The mean $\dot{V}/\dot{Q}$ ratio correspondingly decreased from apex to base at the same time. Both $\dot{V}$ and $\dot{Q}$ were significantly redistributed ($p < 0.05$ to $p < 0.001$) in the miners' lungs relative to those of the controls: reductions in the lower third, and increases in the upper two-thirds of the lungs. This was accompanied by reductions in the regional distribution of the miners' $\dot{V}/\dot{Q}$ ratios in the upper half of both lungs.

The mean HI value for the twenty miners, indicative of heterogeneous ventilation, was 0.190 ± 0.027 (range: 0.150–0.270) (fig. 2). A similarly determined mean HI value for the controls was 0.133 ± 0.011 (range: 0.109–0.149). The HI values for the miners were statistically greater than those of the controls at the level of $p < 0.001$, only one miner falling into the normal (mean $\pm$ 2 SD) range. Although there was considerable overlap of the perfusion HI values for the miners and controls, with respective means of 0.206 ± 0.022 and 0.164 ± 0.041, their difference was statistically significant ($p < 0.001$). The difference in HI for the $\dot{V}/\dot{Q}$ ratio between the miners and controls did not attain statistical significance. The degree of heterogeneous ventilation correlated positively ($r = 0.72$; $p < 0.001$) with $P(A-a)O_2$, an overall measure of gas exchange (fig. 3).

Discussion

Functional pulmonary impairment, which could be quantitated, was found in all twenty West Virginia coal miners examined. Nineteen miners had impaired gas exchange; in addition, four had minimal airway obstruction and five had small airway obstruction, three had abnormal chest radiographs and seven had small airway obstruction as well as abnormal chest radiographs. Sixteen of the subjects also had abnormal scintigraphic studies. Since this was not an epidemiological study, we do not claim a direct relationship between the measured pulmonary function values and the extent of coal exposure. Furthermore, our subjects were not necessarily representative of all West Virginia coal miners at risk, so that the results of this study can only be applied directly to a population with similar characteristics. On the other hand, this group of selected subjects was studied systematically and in great detail using a variety of methodologies, including the use of radiotracers, to elucidate the type and extent of their functional pulmonary impairment, especially in the absence of radiographic or spirometric changes. We suggest that this has allowed us to lay the basis for the development of a very sensitive, objective index (HI) to quantitate impairment.

We found that impaired gas exchange, including irregularities in regional distributions of ventilation and perfusion, was the most significant functional measurement. Although the mean Pa_{O_2} in our group was 86 ± 10 mmHg, which is similar to the results of MORGAN *et al.* [28], gas exchange alone was abnormal in all but one miner. Four miners were hypoxic,

Table 4. - Results of miners' gas exchange and HI measurements

Subject	P_{aO_2} mmHg	$P_{(A-a)O_2}$ mmHg	P_{aCO_2} mmHg	DLCO % predicted	HI	
					Ventilation	Perfusion
1	84	23	35	77	0.196	0.182
2	63	70	24	82	0.226	0.207
3	80	27	41	108	0.157	0.195
4	81	30	30	99	0.211	0.190
5	79	27	39	127	0.205	0.211
6	83	31	34	45	0.171	0.191
7	82	27	36	96	0.182	0.185
8	94	16	35	124	0.181	0.237
9	92	19	33	104	0.184	0.174
10	88	17	33	150	0.150	0.218
11	88	18	35	150	0.169	0.212
12	88	30	31	140	0.193	0.205
13	70	41	31	111	0.222	0.207
14	91	22	31	123	0.173	0.225
15	90	15	36	43	0.170	0.192
16	83	33	33	89	0.196	0.191
17	91	25	34	163	0.270	0.268
18	95	19	37	120	0.173	0.187
19	82	32	34	157	0.196	0.202
20	111	25	30	96	0.181	0.233
$\bar{x}$	86	27	34	110	0.190	0.206
SD	±10	±12	±4	±34	±0.027	±0.022

twelve had a widened $P(A-a)O_2$, twelve were hyperventilating (reduced P_{aCO_2} and increased alveolar ventilation), and three had reduced DLCO. The most notable finding of this study was that we were able to correlate the results obtained from overall arterial blood and air samples with those obtained with a very sensitive technique using a computer analysis of the pixel-by-pixel regional distribution of $\dot{V}/V$ measured with Kr-81m and Xe-127. Since simple CWP is characterized by relatively small, but widespread, focal damage, the degree of heterogeneous ventilation obtained from averaging all the hundreds of individual pixel values throughout the lung could therefore be related directly to the subject's $P(A-a)O_2$. The miners with the widest O_2 gradients also had the most heterogeneous distributions of $\dot{V}$. What was even more important was the fact that seven of the eight miners with normal $P(A-a)O_2$ had a greater ventilation HI than the healthy volunteers, whose values are shown in the lower left-hand corner of figure 3.

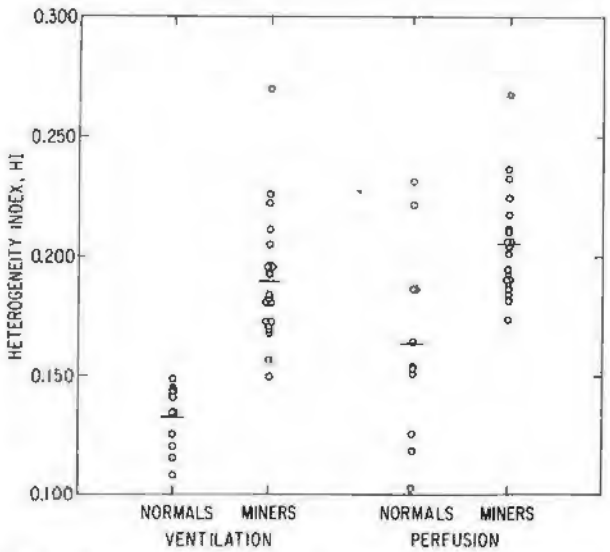

Fig. 2. Comparison of HI values for nonsmoking coal miners and healthy subjects. Mean ventilation value of 0.190 ± 0.027 (range: 0.150–0.270) for coal miners was significantly greater ($p < 0.001$) than 0.133 ± 0.011 (range: 0.109–0.149) for the age-matched controls. Mean perfusion value of 0.206 ± 0.022 (range: 0.174–0.268) for coal miners was significantly greater than 0.164 ± 0.041 (range: 0.103–0.232) for the controls ($p < 0.001$).

In addition to these point-by-point measurements of ventilation, we found that the topographical distribution of $\dot{V}$, corrected for lung volume, was significantly reduced only in the lower lung region of our subjects. This differed from the results of ROBIENCE *et al.* [32], who measured $\dot{V}$ with Xe-133 in twenty-five working miners, and found a reduction only at the apices. In an earlier study of six miners with Xe-133, YERNAULT and ROBIENCE [39] found no ventilatory derangement at all. These differences between their results and ours are probably related to our combined use of Kr-81m and Xe-127 and a large-field-of-view gamma camera. We also found a redistribution of $\dot{Q}$ from the base towards the apex of

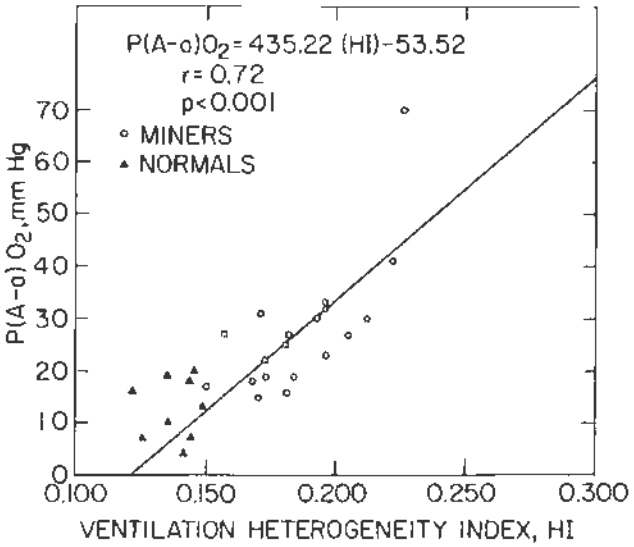

Fig. 3. Correlation of alveolar-arterial oxygen gradient and ventilation heterogeneity index for coal miners. Values for the controls are shown in lower left corner. (Result for subject No. 17 was not included.)

our miners, which is similar to the study of ROBIENCE *et al.* [32]. On the other hand, YERNAULT and ROBIENCE [39] found a reduction in $\dot{Q}$ in the apices of 16/20 miners. WORTH *et al.* [38] found alterations in $\dot{Q}$ in 9/30 miners with normal spirometry, while MICHAELOV *et al.* [25] found a relationship between abnormal $\dot{Q}$ and radiographic or spirometric changes. RASMUSSEN *et al.* [30] have suggested that the pulmonary capillary bed is reduced in some miners with simple CWP. However, our results are in agreement with SEATON *et al.* [34], who found that only 2/21 miners with simple CWP had avascular zones related to the nodules. Although obliteration of pulmonary vessels is common in complicated CWP, relatively few subjects with simple CWP showed significant changes in their lung vascular bed at autopsy [37].

The miners' respiratory symptoms were assumed to be caused by coal dust since they had an extensive exposure history and no other abnormalities were found to explain them. It is important to note that all of them were life-long nonsmokers, so that the effect of cigarette smoke either by itself or in synergism with coal dust could be eliminated as a potential factor influencing the results. This finding is in agreement with the studies of JACOBSEN [19] and others [9, 14, 23], who found significant associations between exposure to coal dust and CWP in nonsmoking coal miners. The role of smoking on the dose-response relationship between CWP and coal dust has been documented by JACOBSEN *et al.* [18].

On the other hand, MORGAN [27] and ROM *et al.* [33] suggested that the effect of cigarette smoke is more significant than that of coal dust in causing pulmonary impairment. Morgan concluded that, while coal dust may lead to the development of industrial bronchitis and minor abnormalities of large airway function, cigarette smoking is between six and ten times more important. Rom and his associates differentiated between the effects of smoking and exposure to coal dust on the impairment of pulmonary function. They found no significant association among nonsmoking miners between exposure to coal dust and changes in pulmonary function. Spirometric results were either normal or only mildly obstructive. However, only forced expiratory measurements were made. No other functional studies, such as measurement of gas exchange, for example, were carried out. MORGAN *et al.* [28] found, in a study of fifty coal miners referred for evaluation of blood gases at rest and during exercise, that only two met the criteria for disabling respiratory impairment. They concluded that blood gas analysis was unnecessary in the determination of disability. In contrast, RASMUSSEN [31] and other investigators [32, 35] found gas exchange abnormalities, even in the absence of impaired ventilatory function. Our results are in agreement with the latter group.

Our results agree with those of ROBIENCE *et al.* [32] and MORGAN *et al.* [28], who found that simple CWP does not result in a significant decrease in overall ventilatory function. Exposures to coal dust in underground mines, ranging from 26–45 yr, produced no obstructive involvement of the large airways in sixteen miners. On the other hand, we found measurable functional impairment of the small airways in sixteen of the twenty miners. These findings were also confirmed by the $\dot{V}$ and $\dot{Q}$ studies. Whilst abnormalities were found in Kr-81m and Xe-127 images, these were generally peripheral $\dot{V}$ irregularities, rather than segmental defects, with minimal Xe-127 retention during gas washout. Although ventilation HI correlated with $P(A-a)O_2$, the miners' ventilation HI did not correlate with measures of overall airway obstruction, such as FEV_1 or $FEF_{25-75\%}$.

In summary, we found gas exchange to be the most significant functional measurement, being impaired in 19/20 nonsmoking coal miners. In contrast, conventional spirometric measurements were within the predicted normal limits for all but four miners. Overall gas exchange measurements, expressed as $P(A-a)O_2$, were correlated significantly ($r=0.72$; $p<0.001$) with the degree of heterogeneity in the pixel-by-pixel regional distribution of $\dot{V}/V$ from radioactive tracer data. Measurement of ventilation and perfusion heterogeneity (HI) appears to be a very sensitive, objective, and noninvasive diagnostic indicator of subtle pulmonary changes in coal miners.

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RÉSUMÉ: Vingt mineurs de la Virginie de l'Ouest, n'ayant jamais fumé, ont fait partie d'une étude visant à mettre en évidence le rôle des lésions pulmonaires sur la ventilation ($\dot{V}$) et sur la perfusion ($\dot{Q}$) régionales et à obtenir une méthode plus fiable pour la détection précoce de la pneumoconiose des mineurs de charbon. Leur âge moyen est de 59.3 ans et leur exposition à la poussière de charbon de 35.2 ans en moyenne. Les tests classiques de la fonction pulmonaire sont complétés par la mesure de $\dot{V}$, $\dot{Q}$ et du volume pulmonaire (V), respectivement à l'aide du Kr-81m, du Tc-99m MAA et de l'Xe-127, afin de déterminer les anomalies régionales de la fonction pulmonaire. Une analyse par ordinateur des distributions régionales de $\dot{V}/V$, $\dot{Q}/V$ et $\dot{V}/\dot{Q}$ est effectuée; leurs distributions topographiques, ainsi que les index d'hétérogénéité (IH) ont été calculés. $\dot{V}/V$ et $\dot{Q}/V$ sont significativement réduits dans le tiers inférieur et augmentés dans les deux tiers supérieurs des poumons de mineurs; $\dot{V}/\dot{Q}$ est réduit dans la moitié supérieure. Les $\dot{V}/V$ et $\dot{Q}/V$ des mineurs sont plus hétérogènes ($p < 0.001$) que ceux de onze sujets témoins appariés, avec respectivement des valeurs IH de la ventilation moyenne de l'ordre de 0.190 ± 0.027 et de 0.133 ± 0.011, et avec des valeurs IH de perfusion moyenne respectivement de 0.206 ± 0.022 et 0.164 ± 0.041. La $P(A-a)O_2$ est en corrélation positive ($r = 0.72$; $p < 0.001$) avec les IH de ventilation. Les échanges gazeux sont la mesure fonctionnelle la plus significative: il sont anormaux dans 19 cas sur 20. En revanche, les mesures spirométriques classiques restent dans les limites normales prédites chez tous les mineurs sauf quatre.