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Background: Exercise impairment is common in subjects with asbestosis. Arterial oxygen desaturation during exercise is an important contributor to exercise limitation. The International Labour Office (ILO) classification of plain chest radiographs correlates with resting pulmonary function, but its value in predicting abnormal ventilatory responses to exercise, including desaturation, has not been explored.

Aims: To determine in subjects with asbestosis (1) if radiographic profusion scores and the extent of small irregular shadows on plain chest radiographs correlate with resting lung function and abnormal ventilatory responses to exercise; and (2) if radiographic scores add value to resting lung function tests in predicting abnormal ventilatory responses to exercise.

Methods: Thirty eight male subjects with asbestosis were included. Plain chest radiographs were read according to the ILO classification independently by three observers. All subjects underwent assessment of lung function and an incremental exercise test.

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Results: Profusion scores and number of affected zones correlated significantly with the percentage predicted values of single breath diffusing capacity (DLCO), forced vital capacity (FVC), and total lung capacity (TLC). Arterial oxygen desaturation occurred in 29% of the subjects. The severity of desaturation correlated significantly with profusion and the number of affected zones. The combined use of number of affected zones, FEV1/FVC ratio and DLCO predicted desaturation during exercise with an explained variance of 41%. VO₂max was significantly related only to DLCO but was not predicted by the ILO score.

Conclusion: Arterial oxygen desaturation correlated with the profusion and extent of parenchymal abnormality on chest radiographs. The addition of morphological indices to physiological measurements is valuable for predicting oxygen desaturation during exercise but not for $VO₂$ max. Refinement of the radiographic scoring system and the addition of more sophisticated imaging techniques may further improve the predictive power.

Sbestosis is a chronic fibrotic lung disease caused by

40 000 individuals in the United States developed

ashestosis between 1968 and 1990² Although the global proinhalation of asbestos fibres.¹ It was estimated that over asbestosis between 1968 and 1990.² Although the global production of asbestos has decreased, the typical long latency between exposure and disease manifestation means that new cases continue to present. Also, while asbestos consumption in developed countries is restricted, its use in developing economies continues to rise.¹ Hence, asbestosis remains a global health issue.

Asbestosis results in functional impairment as a result of restrictive lung defects. Exercise impairment in asbestosis is characterised by arterial oxygen desaturation and a reduction in maximal oxygen uptake (VO, max) .³⁴ Desaturation is an important feature of interstitial lung disease. Not only is it a sensitive indicator of disease severity, but recent evidence suggested it may also have a role in predicting disease progression.⁵ More importantly, oxygen desaturation is an underlying cause of exercise impairment.⁶ Correction of the arterial hypoxaemia with supplementary oxygen has been shown to significantly improve the exercise limitation.⁷⁸ Attempts to predict desaturation and VO₂max using resting lung function have met with limited success,⁹ in part because abnormalities of gas exchange may only become evident during exertion as increased ventilation-perfusion mismatch supervenes. Since these functional problems are the consequences of disease of lung parenchyma, they might be expected to correlate with and be predicted by measures of the intensity and extent of parenchymal disease.

The profusion score of small irregular opacities on plain chest radiographs (CXR) quantified using the International Labour Office (ILO) Radiographic Classification for Pneumoconiosis¹⁰ is a measure of morphological changes within the parenchyma and has been shown to correlate with resting pulmonary function.¹¹⁻¹² However, the value of such radiographic scores in predicting ventilatory response during exercise, either independently or in combination with lung function tests, has not been explored.

The aims of this study were to determine if the profusion scores and extent of parenchymal disease on CXRs of subjects with asbestosis: (1) correlate with resting lung function and abnormal ventilatory responses to exercise; and (2) add value to resting lung function in predicting abnormal ventilatory responses to exercise. We hypothesised that arterial oxygen desaturation is common in subjects with asbestosis and could be predicted from the profusion score and the area of the lung affected on CXRs in patients with asbestosis.

METHODS

Subjects with asbestosis were recruited from the respiratory clinic of Sir Charles Gairdner Hospital, which is the main tertiary referral centre for ex-Wittenoom asbestos miners in

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Abbreviations: CXR, chest radiograph; DLCO, single breath diffusing capacity; FEV, forced expiratory volume; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILO, International Labour Office; PA, posteroanterior; SEE, standard error of the estimate; TLC, total lung capacity; VC, vital capacity; VCO₂, CO₂ output; Vd/Vt, physiological dead space-tidal ratio; Ve, minute ventilation; VO₂, oxygen uptake; Vt, tidal volume

Western Australia. Only subjects who could perform a maximal exercise test were included. Asbestosis was diagnosed on the basis of a history of significant asbestos exposure over at least six months, presence of crackles on auscultation, and evidence of interstitial fibrosis on high resolution computed tomography (HRCT) of the chest, as determined by independent radiologists. Medical and occupational histories were obtained followed by a physical examination. A symptom score based on subjective grades (0–6) of breathlessness were recorded from case notes as described by Agusti and colleagues.5 All subjects underwent measurements of lung function, arterial blood gases, CXR, and a maximal exercise test.

Lung function

Lung volumes were measured by a volume displacement plethysmograph (Model 09103; Warren E. Collins Inc., Braintree, MA, USA), using methods described by Finucane and Mead.13 Maximum expiratory flow volume relation and FEV₁ were measured by pneumotachograph (Model 400VR, Hewlett Packard, Waltham, MA, USA) using methods recommended by the American Thoracic Society.¹⁴ Single breath diffusing capacity (DLCO) was measured by the single breath method (Model 1182, PK Morgan, Chatham, Kent, UK), following the American Thoracic Society recommendations,¹⁵ and corrected for alveolar volume (KCO). Measured values were expressed as a percentage of the predicted normal value (%pred). Reference equations for total lung capacity (TLC) were obtained from Crapo and colleagues,¹⁶ vital capacity (VC) from Kory and colleagues, 17 FEV₁ from Cotes and colleagues, 18 and DLCO from Miller and colleagues.¹⁹

Exercise test

All subjects underwent an incremental exercise test on an electronically braked cycle ergometer (Model ER900, Jaeger, Würzburg, Germany). Workload was increased by 15 watts each minute until the subject achieved his predicted maximal heart rate or was limited by symptoms. Breath by breath measurements of oxygen uptake $(VO₂)$, $CO₂$ output $(VCO₂)$, minute ventilation (Ve), tidal volume (Vt), breathing frequency, inspiratory time, total breath time, respiratory exchange ratio ($R = VCO₂/VO$), and physiological dead spacetidal ratio (Vd/Vt) were measured continuously (Morgan Benchmark Exercise Test System, PK Morgan Ltd, UK). Arterial oxygen saturation was monitored by a pulse oximeter (Biox 3700, Ohmeda, Boulder, CO, USA) using an ear probe. Desaturation of $\geq 3\%$ was considered significant. Heart rate was monitored using a Medeci M-1 cardiac monitor (PK Morgan Ltd). VO, max and maximal heart rate were chosen as the highest VO₂ or heart rate recorded for any 30 seconds of exercise. An exercise test was considered maximal when the subject achieved either 80% of the predicted maximal heart rate or 75% of predicted maximal voluntary ventilation. Equations for predicted maximal workload and VO₂max were obtained from Jones and colleagues²⁰ and Blackie and colleagues,²¹ and for predicted maximum heart rate from Åstrand and colleagues.22 Two measures of ventilation at submaximal exercise were calculated: (1) minute ventilation at an oxygen uptake of 1 litre per minute (Ve1.0); and (2) minute ventilation at 50% of maximal oxygen uptake (Ve50%). All equipment was calibrated prior to each measurement.

Chest radiographs and ILO scores

Standard posteroanterior (PA) CXRs were read, according to the ILO Radiographic Classification for Pneumoconiosis independently, by three experienced observers (YCL, SCP, and AWM). The median reading for each film was used for analysis. A score of 1 to 11 was ascribed for profusion as shown in table 1. The area of the lung affected was quantified by dividing each lung into three zones—upper, middle, and lower—

and ascribing a score between 0 and 6 for the number of zones affected in both lungs. Pleural thickening was scored 0 to 9 for each hemithorax. A score of 0 indicated an absence of thickening. Scores 1–3 indicated the presence of thickening of $<$ 5 mm wide extending over $<$ 25% (score = 1), 25–50% (score $= 2$), and $>50\%$ (score $= 3$) of the lateral chest wall respectively. Scores 4–6 and 7–9 indicated thickening 5–10 mm wide and >10 mm wide respectively, over the same extent categories. The cumulative pleural score of both hemithoraces was used for analysis. A categorical variable was used to indicate the presence or absence of calcification within pleural plaques and obliteration of each costophrenic angle.

Statistical analysis

The univariate relations between symptoms score, lung function, ILO scores, and results of exercise tests were examined using Pearson's correlation coefficient. To identify the important predictors of the dependent variables VO, max and arterial oxygen desaturation during exercise, stepwise multiple linear regression analyses were performed. The joint associations of the four different groups of explanatory variables (demographics, resting lung function, radiographic signs, and blood gases) with exercise response (desaturation and VO, max) were examined in a systematic fashion: first each group of variables was entered into regression models singly and together, then those variables that were significant at p<0.15, either alone or with any of the others, were entered into

regression models with variables from the other groups. All variables that altered the fit of any model at $p<0.15$ were included in the two final "best" models for desaturation and VO₂max separately. The variability about a regression equation was expressed as the standard error of the estimate (SEE), and the percentage of total variance accounted for by the independent variables was reported as the square of the correlation coefficient (R^2) . When there is only one independent variable, this is just the square of the simple Pearson's correlation coefficient. The goodness of fit was evaluated by examining the R^2 . The 5% level of probability was accepted as significant. Data were analysed using Sigma Stat V2.03 statistic software (Jandel Scientific, San Rafael, CA, USA).

RESULTS

Thirty eight subjects with a mean age of 67 years (range 55–78) were recruited. All were white males without other significant medical conditions. Most subjects were former workers in the crocidolite industry at Wittenoom, Western Australia. Twenty nine subjects were ex-smokers, and two were current smokers.

ILO scores

The technical quality of the CXRs were good (grade 1) in 33 subjects and acceptable (grade 2) in five. Table 1 summarises the distribution of scores for profusion, type of small opacity, number of zones affected, and pleural thickening. All subjects have radiological evidence of pulmonary fibrosis on HRCT. In 13 subjects, there was no evidence of interstitial lung disease on CXR (profusion 0/0 or 0/1). Costophrenic angles were obliterated in 10 subjects (four unilateral and six bilateral).

Lung function and exercise test

Table 2 summarises the results of lung function and exercise tests. Although the mean reductions in lung volume and transfer factor were relatively mild, there was a wide range in TLC (32.3–118.7%pred) and DLCO (21.9–126.9%pred). During the exercise test, 30 subjects achieved a maximal test on the basis of ventilatory criteria with or without heart rate criteria, and the remaining eight subjects achieved a maximal test on the basis of heart rate criteria alone. Twenty three subjects stopped because of dyspnoea, 10 because of fatigue, and five because of joint pain.

Eleven subjects (28.9%) experienced arterial oxygen desaturation during exercise, and this was in the range 3.0–5.9% in six, $6.0-8.9\%$ in one, and $>9.0\%$ in four. Two subjects who desaturated had no evidence of interstitial lung disease on plain radiographs (profusion scores 0/0 or 0/1).

DLCO correlated significantly with VO₂max ($r = 0.57$, p < 0.001), and inversely with arterial oxygen desaturation during exercise (*r* = −0.47, p < 0.01), Ve1.0 (*r* = −0.61, $p < 0.001$), Ve_{50%} ($r = -0.40$, $p = 0.02$), and Vd/Vt ($r = -0.74$, $p < 0.001$). There were weaker correlations between VO, max and FEV₁ ($r = 0.36$, $p = 0.03$) and TLC ($r = 0.36$, $p = 0.03$). In our cohort, the formula previously suggested by Cotes and colleagues⁹ for predicting VO, max %pred from lung function and ventilation at submaximal exercise (VO₂max %pred = 0.44 FEV₁ %pred − 0.78 Ve1.0 + 0.16%DLCO + 52.3) explained only 22% of the variance in VO, max %pred.

Relation between ILO scores and lung function

Table 3 summarises the relations between ILO scores and lung function. Profusion score correlated significantly and inversely with FEV₁, FVC, TLC, and DLCO. The number of zones affected correlated inversely with FVC, TLC, and DLCO. Pleural thickening score correlated inversely with $FEV₁$, FVC, and TLC. The alveolar-arterial (A-a) oxygen gradient correlated directly with the profusion score.

Relation between ILO scores and ventilatory response to exercise

Table 4 summarises the relations between ILO scores and the ventilatory response to exercise. The profusion score, number of zones affected, and predominance of "t" opacities all correlated with arterial oxygen desaturation during exercise and Vd/Vt at peak exercise. The profusion score and predominance of "t" opacities also correlated with Ve1.0 and negatively with VO₂max. There was no significant correlation between pleural thickening and the ventilatory response to exercise.

Relation between symptom score and lung function, ILO scores, and ventilatory response to exercise

Symptom score correlated negatively with DLCO. There was no correlation between the symptom score and other measures of lung function, ILO scores (table 3), desaturation $(r = 0.13, NS)$, or other measures of ventilatory response to exercise.

Prediction of arterial oxygen desaturation during exercise and VO₂max

The correlation between desaturation and VO₂max was -0.20 $(p = 0.23)$. Smoking, age, and body mass index were unrelated to either exercise measure. While VO, max was associated with each of $FEV₁$, FVC, and TLC when taken singly, once the association with DLCO was controlled, there was no added association with other measures of lung function. For desaturation, however, while DLCO was also the strongest predictor, the FEV₁/FVC ratio was also strongly predictive $(R² = 0.30)$. From *x* ray signs, both the level of profusion and the number of zones were independently associated with desaturation ($R^2 = 0.36$), whereas only the level of profusion was predictive of VO_2 max. Blood gas measurements were unrelated to VO₂max and only A-a gradient was independently predictive of desaturation. When all the measures were combined, arterial oxygen desaturation during exercise was best predicted by the equation: arterial oxygen desaturation (%) = 1.05 + 0.07*A-a gradient + 0.07*FVC%pred − 0.09*TLC%pred + 0.82*number of zones affected ($R^2 = 0.45$, SEE 2.4). In the absence of blood gas measurements, the best fitting equation was: arterial oxygen desaturation $(\%) = -1.24$ + 0.06*FEV₁/FVC ratio – 0.04*DLCO%pred + 0.77*number of zones affected ($R^2 = 0.41$, SEE 2.5).

VO₂max %pred was best predicted by DLCO alone, using the equation VO, max %pred = $32.2 + 0.51*D_{LCO}$ %pred $(R^2 = 0.31, SEE 17.4)$. The residual variance was not explained by other measures of lung function, ILO scores, and ventilatory response to submaximal exercise.

Table 3 Correlation (Pearson's coefficient) between ILO score, lung function, and symptom score

Table 4 Correlation (Pearson's coefficient) between ILO score and ventilatory response to exercise

DISCUSSION

This study showed that arterial oxygen desaturation during exercise was common in subjects with asbestosis. Desaturation correlated with the extent and severity of radiographic parenchymal abnormalities quantified using ILO scores, but not with symptoms. The combined use of morphological indices (number of affected zones) and physiological measurements (TLC, FVC, or DLCO and FEV₁/FVC) predicted desaturation during exercise. In contrast, VO₂max was significantly related only to DLCO and was not predicted by the ILO score.

Asbestosis is a known hazard of occupational exposure to airborne asbestos fibres. In the United States, over 40 000 workers were diagnosed with asbestosis between 1969 and 1990,² and 8761 deaths were certified as resulting from asbestosis between 1979 and 1992.¹ In Western Australia, 2.6% of the former workers in the Wittenoom crocidolite industry have developed compensatable asbestosis.²³

Measurement of functional impairment in subjects with asbestosis is important for patient management and prognosis as well as for medicolegal issues. In these subjects, exercise limitation typically results from the pulmonary and pleural fibrosis. Arterial oxygen desaturation and $VO₂$ max measured during exercise testing are parameters commonly employed to measure functional impairment^{3 4 24} which relates closely to the degree of disablement. Desaturation is significant because arterial hypoxaemia underlies exercise limitation in interstitial lung disease, 7 ⁸ and treatment with supplementary oxygen has been shown to improve exercise capacity. Desaturation is also a sensitive indicator of interstitial lung disease,⁴ and can predict disease progression.

Desaturation was seen in as many as 29% of the participants in the present study, even though the subjects included had relatively mild disease. However, predicting which of the subjects with asbestosis will desaturate during exercise is difficult. Our data showed that self reported symptoms were poor indicators of exercise desaturation. Objective measures to help identify subjects who experience desaturation during exercise have seldom been studied.

The ILO scoring system is a validated method for quantification of parenchymal and pleural involvement from pneumoconiosis on plain chest radiographs,¹⁰ and is frequently used in clinical settings and epidemiological studies.³ ²⁵⁻²⁷ The ILO system allows measurement of the intensity (profusion score), and the extent of damage (number of zones involved) from asbestosis. Our data confirmed that the ILO scores were associated with abnormalities in resting lung function. Restrictive pulmonary changes (reduced TLC, FVC, and DLCO) correlated with the intensity and the extent of parenchymal involvement as shown on CXRs.

The relation between ILO scoring and exercise performances, especially oxygen desaturation, in asbestosis has not been explored before. We found that both profusion score and the number of zones affected are associated with desaturation. More importantly, desaturation predicted arterial oxygen desaturation independently of any parameter in the resting lung function testing, including DLCO. However, the addition of DLCO to ILO scores did improve their prediction of oxygen desaturation, suggesting that the severity of interstitial lung disease can be more accurately reflected by combined consideration of both functional and radiographic data.

Most previous studies on the relation of ILO scoring and pulmonary function have focused on the use of profusion.3 26 28 Our data show that in addition to the profusion score, the area of the lung affected by small opacities also correlates with functional abnormalities, illustrating the importance of considering the extent of disease involvement. This point is similarly emphasised in recent studies using high resolution computed tomography (HRCT) in patients with cryptogenic fibrosing alveolitis or with pulmonary fibrosis secondary to scleroderma.²⁹⁻³¹ In the ILO classification, each lung is divided into three zones and the extent of disease is quantified as the number of affected zones.¹⁰ In spite of the ILO classification being considerably less sophisticated than HRCT in determining the extent of lung parenchyma affected, the correlation between the extent of disease and desaturation achieved in our study with plain CXRs is comparable to those using HRCT.^{30 31} It is likely that these relations can be strengthened if a more precise method of quantifying the extent of disease involvement on CXR is used.

The profusion score was obtained from the area of the lung with the highest concentration of small opacities, and

frequently there was considerable inhomogeneity among different areas of the lung. A system of averaging the profusion score over both lungs may be more representative of overall disease severity and may better reflect functional abnormalities.

In this study, the profusion score correlated directly with oxygen desaturation and minute ventilation at submaximal levels of exercise, and negatively with maximal oxygen uptake. There was no relation between pleural disease and the ventilatory response to exercise. These findings are in keeping with those of Cotes and colleagues.⁹ However, in that study, 71% of the variability in VO, max %pred was explained by combined measures of $FEV₁$, DLCO, and minute ventilation at an oxygen uptake of 1.0 l/minute. In our cohort, these variables explained only 22% of the variability in VO, max %pred, and VO,max was best predicted from DLCO alone. These discrepancies may partly be caused by the different selection criteria in the two studies. Our subjects were selected on the basis of the presence of interstitial disease on HRCT, while the presence of abnormal lung function and an exercise test limited by breathlessness were not mandatory. Our cohort thus represented a group who had milder disease. These findings highlight the fact that exertional breathlessness and VO₂max in subjects with asbestosis are determined by multiple factors, many of which are unrelated to asbestos lung disease³² and are not necessarily reflected in measures of lung function or ILO scores.

Quantification of pulmonary involvement of asbestosis using CXRs (and ILO system) has advantages and disadvantages when compared with more advanced imaging modalities such as HRCT. While HRCT can measure the extent of parenchymal damage more accurately,³³ it is difficult to quantify the intensity (profusion) of disease on HRCT. Also, CXRs are cheaper and more accessible—important considerations in population or work force screening of interstitial lung diseases. The use of HRCT however allows the quantification of coexisting emphysema, which is grossly inaccurate from CXRs. Smoking related lung diseases are common in subjects with asbestosis,²³ and the inclusion of extent of emphysema has been shown to improve the power of HRCT scoring in predicting exercise impairment.³⁰

In our study, pleural thickening was associated with reduced lung volumes and DLCO (as had been shown by oth $ers³⁴⁻³⁵$), but the extent of pleural involvement did not correlate with abnormal ventilatory response to exercise. HRCT may also allow better visualisation of the pleura and quantification of pleural involvement. Pleural fat can produce apparent pleural thickening on CXRs in obese individuals,³⁶ and HRCT can provide more definitive differentiation between adipose tissue and pleural fibrosis.

While the number of subjects in our study is small and the findings require confirmation in larger studies, we believe that the results presented are important. In summary, both the severity and the extent of asbestosis involvement on plain chest radiographs are independent predictors of arterial oxygen desaturation during exercise, but only the extent of involvement adds to the predictive information provided by static lung function tests in this cohort. When evaluating the severity of asbestosis, both the profusion and the number of zones affected should be considered.

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Main messages

- Arterial oxygen desaturation is common in subjects with asbestosis.
- The severity of desaturation during exercise correlated significantly with the profusion scores and the extent of lung parenchymal involvement on plain chest radiographs.
- Combining the radiological and physiological indices can improve the power of predicting desaturation during exercise in subjects with asbestosis.
- Refinement of the radiographic scoring system and the addition of more sophisticated imaging techniques may further improve the predictive power.

Policy implication

• Both the profusion and the number of affected zones should be considered when evaluating the severity of asbestosis.

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