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1. BACKGROUND

Silicosis, a silica-induced inhalational occupational disease, characteristically produces nodular changes on chest radiographs. Currently there is no gold standard to quantitatively measure the degree of respiratory incapacity in silicosis sufferers for the purpose of awarding industrial compensation. Many Western countries use a combination of clinical parameters, lung function studies and the International Labour Organisation (ILO) 1980 International Classification of the radiographic appearances of pneumoconiosis to assess for the presence and extent of silicosis [1]. In Hong Kong, the Pneumoconiosis Compensation Ordinance (PCO) employs an 11-point scale based on the predicted forced vital capacity percentage (FVC%) to assess the degree of incapacity suffered. This method is an over-simplication in comparison to other methods used.

A poor correlation exists between lung function tests and nodular profusion on chest radiographs [2-4]. The superiority of computed tomography (CT), and high resolution computed tomography (HRCT), over chest radiograph in evaluating interstitial and parenchymal lung disease is well-described by the Principal Investigator and other workers [5-7]. CT features of asbestosis are well established with CT being routinely used in the evaluation of the lung in asbestos workers in Quebec [10]. The utility of CT in silicosis has largely been limited to work published from North America [3,4,8-11]. Most of these studies have applied the ILO classification, with some modifications, to grade nodules on CT [3,8-10]. There have been conflicting reports on the correlation of lung function with CT grades of silicosis, with some studies describing positive association between nodularity and coalescence with deteriorating lung function [3,11], whilst others have found no such correlation [4].

Emphysema in silicosis is thought to be associated with progressive massive fibrosis (PMF) although other causative factors like smoking and mineral dust exposure coexist in silicosis sufferers [9-11]. Some workers believe that silicosis per se without PMF does not contribute to emphysema [9-11]. In the ILO classification, emphysema is not graded although its appearance is noted. It has also been suggested that it is the degree of emphysema in silicosis that determines the level of lung function and not the silicotic nodules [4,13]. There have been some studies that have tried to address this issue by grading emphysema on CT according to extent of lung involvement [3,4,10,11]. Although diagnosis of emphysema is often clinical, the assessment of lung function in many of these patients poses a major problem in terms of poor patient co-operation due to physical handicap resulting from concomitant illnesses such as cerebrovascular accident, or to incapacitation secondary to poor respiratory reserve. Other problems that beset lung function testing include poor correlation between clinical performance and lung function indices. HRCT has also been used by the Principle Investigator to detect areas of air-trapping [12], while 3D-CT volumetry has very recently been used for lung volume assessments before and after lung volume reduction surgery [13-14]. Quantitative CT analysis of lung using attenuation thresholds is another method of evaluating emphysema [15-16].

For optimal imaging of silicosis, a combination of 5-10mm conventional CT sections and 1-2mm HRCT sections are advocated [10]. Due to superimposition of tissues, micronodules are better visualised on conventional CT with thicker collimation compared with thinner sections used in HRCT as these may be difficult to distinquish from vessels seen end-on. HRCT however is superior in delineating parenchymal abnormalities particularly within the interstitium. 3D-CT volumetry is performed using non-HRCT data set, which can be transferred to a compatible Graphics workstation and 3D models generated.

This study proposes to apply quantitative CT and 3D-CT lung volumetry in the assessment of silicosis patients. The final objectives are (1) to provide a framework on which a reproducible classification system for nodular profusion and emphysema in silicosis can be devised, (2) to validate 3D-CT volumetry in the functional assessment of silicosis patients, and (3) to compare utility of CT technique with the present DOI system.

1 PROJECT SUMMARY

2.1 Aims

2.1.1 To evaluate the degree of emphysema and nodular profusion in the lungs of patients with silicosis

2.1.2 To study and quantify the inter-correlation between CT grades of emphysema and nodular profusion in silicosis patients with clinical, exercise and lung function parameters

2.1.3 To perform 3D-CT lung volumetry in patients with silicosis to evaluate lung and emphysema volumes

2.1.4 To evaluate the accuracy and utility of 3D-CT lung volumetry by correlating emphysema volumes obtained by the 3D-CT method with lung function indices including spirometry and lung volumes, and with exercise and other clinical parameters

2.1.5 To compare the efficacy of CT methods in evaluating silicosis with present system utilising degree of incapacity (DOI).

2.2 Patient recruitment

A total of 106 men were evaluated with CT according to the protocol attached (appendix I). Fifty-seven patients underwent additional expiratory volumetric scans for 3D-CT. Twenty-six men were excluded from final analysis due to a combination of the following factors: poor image quality and technical difficulties in retrieving CT data (n=8), absent or incomplete lung function data (n=10), missing exercise data (n=8). The data of 85 men were used for the following analysis: 3D-CT (n=52), qualitative and quantitative CT (n=76), and chest radiograph (CXR) evaluation (n=76) according to protocol. Data from the same 76 men were used for qualitative and quantitative CT and CXR evaluation. Correlations with clinical parameters including lung function, exercise parameters and clinical parameters such as smoking history and silica exposure was obtained.

2.3 CT data

Quantitative and qualitative evaluation was performed on the CT films of 76 men. Fifty-seven men underwent 3D-CT evaluation, of these 43 also qualitative and quantitative CT evaluation. Five of the 57 men who underwent additional expiratory volumetric scans for 3D-CT analysis were excluded due to inability to breath-hold adequately.

2.3.1 Qualitative analysis

Only 1 reader was used for visual qualitative grading of nodular profusion and progressive massive fibrosis (PMF) in accordance with previous studies, which have determined that inter-observer error for CT analysis of silicosis was negligible (1,2). Each lung was divided into 3 zones (upper, middle and lower) for evaluation, the total number of zones for evaluation being 6. The grading system for nodular utilised a 5 point grading scale (**0**=no nodules; **1**=small numbers without vascular obliteration; **2**=larger numbers with mild vascular obliteration; **3**=large numbers with moderate vascular obliteration, or 2 with coalescence (<1.5cm); **4**=large numbers with severe vascular obliteration with or without coalescence, or 3 with coalescence. The overall grade of nodular profusion = total score from all 6 lung sections, the maximum scores for any 1 case being 24 (Appendix I). This grading system was modified from that used by Bergin et al (4). PMF, defined as conglomeration of ≥ 1.5cm, was separately graded (**0**=no PMF; **1**=one or more opacities of which the total size is < 5cm, and not extending below the aortic arch; **2**=one or more opacities with total size >5cm not extending below the aortic arch; **3**=one or more opacities extending to level of carina; and **4**=one or more opacities extending to the level of the inferior pulmonary vein. Throughout this report qualitative evaluation of nodular profusion and PMF will be respectively called CT-NP grade and CT-PMF grade.

2.3.2 Quantitative analysis

The CT data of 76 men were transferred to a free-standing workstation (Windows Advantage; GE Medical Systems) and quantitative analysis was performed at 3 selected axial levels as indicated in the protocol to quantify nodular profusion, emphysema, lung density and total lung area using threshold levels. Emphysema was quantified using 2 different higher threshold levels (-910 and –950 HU). The ratio of nodular profusion and emphysema with respect to total lung area was determined and respectively termed nodular profusion index (NPI) and emphysema index (EI). The latter was sub-classified into EI-910 and EI-950 to indicate the 2 different threshold used to quantify emphysema: -910 and –950 HU respectively. NPI and mean lung density were regarded as quantititive measures of nodularity, and CT-NP grade and CT-PMF grade as qualitative measures of nodularity.

2.4 3D CT

Volumetric data from 52 men was transferred to a graphics workstation, where 3D models were reconstructed using 3D shaded-surface display (SSD) technique**.** Threshold limits of -400 to -1024 HU were applied to both inspiratory and expiratory data sets to acquire CT total lung capacity (CT-TLC) and residual volume (CT-RV) respectively. The difference between inspiratory and expiratory volumes approximated the 3D vital capacity (3D-VC). To obtain CT emphysema volume (CT-EV), threshold limits of -910 to -1024 HU was applied to the inspiratory volumetric data. CT emphysema volume corrected for TLC was also obtained for analysis (CT-EI)

2.5 Chest radiographs (CR)

Seventy-six CRs were reviewed independently by a physician Dr CM Tam and a radiologist, Dr Clara Ooi, and graded according to the ILO 1980 classification. Patients were grouped into four categories according to the profusion of nodules as described in the ILO classification: **0**=0/-, 0/0, 0/1; **1**=1/0, 1/1, ½; **2**=2/-, 2/2, 2/3; **3**=3/-, 3/3, 3/+. This was termed the CR nodular profusion score (CR-NP score). Presence of PMF was separately recorded as 1, 2 and 3 according to ILO category A, B, C respectively (CR-PMF score). Consensus opinion was sought when opinions differed by 1 category. Intra-observer analysis was determined.

2.6 Clinical parameters

Dr KWT Tsang and his co-workers at the Department of Medicine conducted this arm of the study. Lung function was incomplete or not performed for one reason or other in 10 men, while exercise parameters were not available in 8 men. Submaximal exercise test was conducted with MedGraphic CardioO_2 package to determine exercise tolerance and sub-maximal oxygen uptake. Dyspnoea was clinically graded using Borg's 12 point scales (0,0.5,1-10). The Pneumoconiosis Fund Board, from their assessment procedures, was able to supply the degree of incapacity (DOI), which is an 11-point grading system ranging from 5% to 100% DOI for 55 men in the qualitative and quantitative study, and 35 men in the 3D-CT study. Hence, for any analysis involving DOI, only the data from these 55 and 35 men only were included. Smoking and occupational exposure was quantified as number of pack-years smoked and years of exposure respectively.

Lung function tests were conducted according to standard protocol recommended by the American Thoracic Society (17), with a SensorMedics 2200 (SensorMedics, Yorba Linda, USA) package. The following lung function parameters were obtained and used for analysis: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, total lung capacity (TLC), residual volume (RV), vital capacity (VC), carbon monoxide diffusion coefficient (DLCO) and DLCO corrected for haemoglobin (DLCO/VA). TLC and RV were obtained using nitrogen washout method following standard guidelines (18). Diffusion capacity was measured using the single-breath carbon monoxide diffusing capacity procedure. Spirometric and lung volume parameters were expressed as a percentage predicted based on prediction equations of Da Costa (19), while predicted values for diffusion parameters were based on Cotton

Dust Standard as described in the Operator's Manual (20-22). All lung function data quoted represented % predicted values. An obstructive lung defect was defined as FEV_1/FVC ratio below the 95% confidence level of normal predicted value; restrictive defect when TLC was below the 80% predicted normal value; and mixed when there was a combination of the 2 defects. All CT parameters in the qualitative and quantitative CT study and 3D-EV and 3D-EI were analysed with all the above clinical parameters.

2.7 Statistical analysis

2.7.1 Qualitative and quantitative CT

Univariate analyses of the associations between clinical parameters with lung function tests, CXR and CT parameters were determined using Spearman's correlation. Clinical parameters included DOI grades, distance walked during 6 minute-walk test, maximal O2 uptake (% predicted) and Borg's grade of dyspnoea, age, number of pack-years smoked and years of silica exposure. NPI, EI-910 and EI-950 were abnormally distributed. The differences between men with and without PMF (based on CT) with respect to CT scores, lung function and other clinical parameters were tested using Mann-Whitney rank sum test and independent t-test where appropriate. Multiple regression analysis was performed to determine which HRCT parameters best predict lung function (FEV1, FVC, FEV/FVC, FEF_{25-75}, TLC and DLco), exercise parameters (6 minute-walk test, maximal O2 uptake), Borg's grade of dyspnoea and DOI, adjusted for smoking (pack years) and duration of silica exposure. NPI was highly correlated with all other CT parameter and it was therefore omitted as an independent variable. Similarly only EI-950 was used as an independent variable representing emphysema in the regression analysis as it was highly correlated with EI-950. CR parameters were not included in the multiple regression analysis with CT parameters as they were highly correlated. Separate multiple regression analysis was performed to determine which CR parameters best predict lung function, exercise and clinical parameters including DOI, adjusted for smoking and duration of silica exposure. Inter-observer agreement for CXR parameters was evaluated using Cohen's Kappa.

2.7.2 3D-CT

The CT-derived TLC and RV were compared with those obtained by standard physiological techniques using the method of analysis suggested by Bland and Altman [23]. These measurements were evaluated for evidence of systematic bias. The difference between the measurements and the 95% confident limits of agreement were also calculated. The relationship between the CT-derived emphysema volume (CT-EV), with and without correction for TLC (CT-EI), and physiological lung function indices and clinical parameters was examined using conventional Pearson correlation analysis. The analysis was performed using SAS System version 6.12. A $p<0.05$ was taken as indicative of statistical significance.

2.7.3. DOI versus qualitative and quantitative CT

To compare the efficacy of CT parameters with that of DOI in defining lung function impairment and exercise intolerance, multiple regression analysis was performed using CT-PMF, mean lung density, EI-950 and DOI as constant variables adjusted for smoking and duration of silica exposure.