Cor pulmonale and silicosis: a necropsy based case-control study

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Abstract

The presence of cor pulmonale at death in relation to other factors such as emphysema, silicosis, and thromboembolism was analysed in a case-control study of 732 South African gold miners. Marked emphysema was the highest risk factor with an odds ratio of 21.32 (95% confidence interval (95% CI) 5.02-90.7), then extensive silicosis (OR 4.95, 95% CI 2.92-8.38) and thromboembolic disease (OR 1.92, 95% CI 1.37-2.69). Age and smoking were not significant predictors of cor pulmonale.

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Cor pulmonale denotes right ventricular hypertrophy secondary to structural or functional abnormalities of the lungs.¹ Right ventricular hypertrophy is a response to pulmonary arterial hypertension that may be the result of vasomotor narrowing of small pulmonary arteries and arterioles or anatomical obliteration of the vascular bed.² Reliable estimates of the prevalence of cor pulmonale are sparse but it has been stated that, beyond the age of 50 cor pulmonale is the third most common cardiac disorder, after coronary and hypertensive heart disease.²

The most frequent cause of cor pulmonale in the general population is considered to be vasomotor increase in pulmonary vascular resistance as a result of alveolar hypoxia consequent on chronic obstructive lung disease—that is, chronic bronchitis, bronchiolitis, and emphysema.³ Although cigarette smoking is the most important environmental aetiological factor associated with chronic obstructive lung disease,⁴ occupational exposures are being increasingly implicated.⁵ Anatomical increase in the pulmonary vascular resistance may be due to

obliteration of the vascular bed by thromboembolic disease or fibrotic processes. Silicosis fits into this last group. In silicosis there is perivascular location of silica dust and fibrosis that results in obliteration of the terminal branches of the pulmonary vasculature⁶ and forms a possible basis for the development of cor pulmonale.

The aim of this study was to determine the contribution of silicosis to the development of cor pulmonale.

Methods

STUDY POPULATION

The study population consisted of white South African gold miners aged 45 and over who underwent a full necropsy between 1974 and 1988. Examination of the cardiorespiratory organs at necropsy is required by law for compensation purposes for all miners and ex-miners who die in South Africa provided the next of kin agrees.⁷ Examination of the cardiorespiratory organs is performed by pathologists at the National Centre for Occupational Health and findings are recorded in a computerised data base known as PATHAUT (Pathology Automation).⁸ Full examination is offered for miners dying within 100 km of Johannesburg, in whom inflation of the lungs and dissection of the heart according to Fulton's technique⁹ are routinely performed. After removal of fat and coronary vessels the atria are separated from the ventricles; the right ventricle (RV) and the left ventricle and the septum (LV + S) are weighed separately. For those dying further afield the necropsy is limited to the cardiorespiratory organs, which have been previously removed and preserved in formalin.

It is estimated that 86% of white South African gold miners who die undergo necropsy.¹⁰ There are no significant differences in age, years of service, and prevalence of pneumoconiosis between men undergoing full and limited necropsies; however, when compared with those who have no examination, those who have necropsy had longer service and had been compensated less often during life.¹⁰ This study was limited to those miners and ex-miners undergoing full necropsies.

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Table 1 Study population and exclusions

Initial population (full necropsy 1975-87)	4226
Excluded subjects:	
Heart mass, RVM or LV + S missing	48
LV + S > 224 g	1917
Valve disease	61
Asbestosis	14
Final study population	2186
Selected cases	391
Selected controls	341
Remainder did not meet criteria for cases and controls	1454

SELECTION OF CASES AND CONTROLS

The original criteria of Fulton *et al*⁹ for right ventricular hypertrophy were applied to define cases. A case was any person with a ratio of LV + S:RV > 2:1 and a right ventricular mass (RVM) > 79 g; LV + S was <190 g. The control subjects had normal hearts—that is, (LV + S):RV of 2:3:1 to 3:3:1, RVM < 65 g, TVM (total ventricular mass) <250 g, and LV + S <190 g.

Because right ventricular hypertrophy may develop secondary to left ventricular hypertrophy, subjects with LV + S > 224 g were excluded from the study (n = 1917). Subjects were also excluded if any valvar abnormality was apparent (n = 61).

Ideally, all subjects with ischaemic heart disease should have been excluded. As most of the study population had this, the number of subjects remaining after exclusion would have been too small for analysis. The proportion of cases with ischaemic heart disease was similar to that of controls and the disease was thus effectively controlled for.

Table 1 shows the selection of the study population. In 48 subjects the weights of the hearts had not been recorded in the data base and these, together with a further 14 subjects with asbestosis, were excluded.

A total of 4226 miners and ex-miners died aged 45 and older and had full necropsies between 1974 and 1988. Of these, 2186 comprised the final population. One thousand four hundred and fifty four subjects were excluded on the basis of RVM between 64 g and 80 g, LV + S > 189 g, TVM > 249 g, and LV + S:RV between 2:1 and 2:3:1 > 3:3:1. These subjects were excluded because they did not fit the strict definitions of a case or control that were applied to ensure clear categories for analysis with no overlap of the characteristics of interest. Thus 391 cases and 341 controls were analysed.

DEFINITIONS

Ventricular hypertrophy

The ratio LV + S:RV provides the most appropriate method of assessing ventricular hypertrophy. A ratio of LV + S:RV < 2:1 indicates indisputable

right ventricular hypertrophy provided that left ventricular hypertrophy (defined as LV + S > 225 g) is absent.⁹

Ischaemic heart disease

Ischaemic heart disease was classified as minimal disease—slight coronary artery atheroma; moderate disease—moderate coronary artery atheroma; and severe disease—pronounced atheroma, extensive myocardial fibrosis, or myocardial infarction.

Silicosis

Silicosis was assessed macroscopically and confirmed microscopically. It was graded as slight, moderate, or extensive, based on the profusion of nodules. Eleven subjects with massive fibrosis were included in the extensive disease category.

Emphysema

The lungs were inflated with 10% formalin at a pressure of 25 cm H₂O and a paper mounted whole lung Gough-Wentworth section¹¹ was made from one lung (usually the right). Emphysema was assessed by a modification of the grid method with 20 radiating zones. The amount of emphysema in each zone was estimated on a scale of 0 to 5, giving a possible total score of 100 (5 × 20). Emphysema was graded as insignificant (<35), moderate (35-65), or marked (>65).

The presence of pulmonary thromboembolism was also recorded. Smoking histories were obtained from PATHAUT and subjects were grouped for analysis into smokers, ex-smokers, and those who had never smoked. Height and last live mass were also used in the description of the study population (table 2).

Results

Table 2 presents the demographic characteristics of the cases and controls. Controls were slightly younger and shorter and weighed less than the

Table 2 Demographic characteristics of cases and controls

	Cases		Controls	p Value
Age (y; mean (range))	66.0	(45-88)	65.6	(45-94) 0.5325
Body mass (kg; mean (range))	70.7	(46-110)	69.1	(41-180) 0.1109
Height (cm; mean (range))	171.9	(136-198)	170.6	(138-200) 0.0178
Smoking state (No (%))				
Smoker	181	46.3	163	47.8
Ex-smoker	89	22.8	65	19.1
Non-smoker	39	10.0	45	13.2
Unknown	82	21.0	68	19.9
Total	391		341	

$\chi^2 = 3.02$, df = 3, p = 0.3891.

Table 3 Frequency of ischaemic heart disease

	Cases No	(%)	Controls No	(%)
Severe	101	(25.8)	80	(23.5)
Moderate	19	(4.9)	31	(9.1)
Minimal	197	(50.4)	160	(46.9)
None	74	(18.9)	70	(20.5)
Total	391		341	

$$\chi^2 = 5.87, df = 3, p = 0.1179.$$

cases. These differences were not statistically significant. Information regarding smoking was unavailable for 20.5% of the study population. The proportion of smokers in both groups was similar (46.3% and 47.8% respectively). A slightly greater proportion of cases were ex-smokers compared with controls; non-smokers were more frequent in the control group (13.2%) than in cases (10.0%). The distribution of smoking state, however, did not differ significantly ($p = 0.3891$).

The presence of ischaemic heart disease was analysed in greater detail as this was thought to be a possible confounder in the analysis (table 3). There was no significant difference between cases and controls in either the presence of ischaemic heart disease or in its distribution by severity of disease ($p = 0.1179$).

Table 4 shows distribution of emphysema, silicosis, and thromboembolic disease. There was a striking difference in the distribution of emphysema between cases and controls ($\chi^2 = 73.35$, $p < 0.0001$). The proportion of cases with marked or moderate emphysema (53.2%) was more than twice that for controls (25.2%). The difference was even greater for the category of marked emphysema alone (9.2% of cases *v* 0.6% of controls).

Both silicosis and emphysema were more preva-

Table 4 Distribution of emphysema, silicosis, and thromboembolic disease in the study population

Disease	Cases No	(%)	Controls No	(%)
Emphysema:*				
Marked	36	(9.2)	2	(0.6)
Moderate	172	(44.0)	84	(24.6)
Insignificant	153	(39.1)	193	(56.6)
None	30	(7.7)	62	(18.2)
Silicosis:†				
Extensive	30	(7.7)	7	(2.1)
Moderate	47	(12.0)	26	(7.6)
Slight	123	(31.5)	98	(28.7)
None	191	(48.8)	210	(61.6)
Thromboembolic disease:‡				
Present	57	(14.6)	12	(3.5)
None	334	(85.4)	329	(96.5)
Total	391		341	

* $\chi^2 = 73.35$, $df = 3$, $p < 0.0001$.

† $\chi^2 = 22.28$, $df = 3$, $p < 0.001$.

‡ $p < 0.0001$.

lent and severe in cases than in controls. Extensive silicotic disease was present in 7.7% of cases and only 2.1% of controls. Thromboembolic disease was four times more prevalent in cases (14.6%) than in the control group (3.5%). Thus it seems that emphysema, silicosis, and thromboembolic disease are highly associated with cor pulmonale at death.

The PC SAS CAT mode procedure was used in the regression analysis to determine the predictors of cor pulmonale. Fulton's ratio was used as the dependent variable in the model. Age at death, smoking state, presence of thromboembolic disease, and severity of emphysema and silicosis were the independent variables. "No emphysema" was included in the insignificant category to compensate for the small numbers.

Age and smoking did not contribute significantly to the model. Emphysema, silicosis, and thromboembolic disease were strong predictors of cor pulmonale (table 5). There was a 1.92 times greater risk of cor pulmonale with thromboembolism; a 2.77 times greater risk with moderate *v* insignificant emphysema; and a strikingly increased risk of 21.32 with marked *v* insignificant emphysema.

A statistically significant association between silicosis and cor pulmonale was found with extensive silicotic disease (odds ratio 4.95; $p = 0.0003$). An odds ratio of 1.63 for moderate silicosis was calculated but this was only marginally significant ($p = 0.0883$). The odds ratio of 1.46 associated with slight silicosis was lower than that for moderate silicosis (1.63) but was statistically significant ($p = 0.0338$).

Discussion

This study has shown a statistically significant association between silicosis and cor pulmonale. Extensive silicosis was present in 7.7% of cases and 2.1% of controls, moderate silicosis in 12% and 7.6%, and slight silicosis in 31.5% and 28.7% of cases and controls respectively (table 4). The difference in distribution of silicosis between cases and controls was statistically significant ($\chi^2 = 22.28$; $p < 0.001$).

Table 5 Odds ratios for the predictors of cor pulmonale

Disease	Odds ratio	95% CI	p Value
Emphysema:			
Marked : insignificant	21.32	5.02-90.70	0.0011
Moderate : insignificant	2.77	1.99-3.87	0.0011
Silicosis:			
Extensive : none	4.95	2.92-8.38	0.0003
Moderate : none	1.63	0.93-2.84	0.0883
Slight : none	1.46	1.03-2.08	0.0338
Thromboembolic disease:			
Yes : no	1.92	1.37-2.69	0.0001

Although standard textbooks¹² and recent review articles^{13,14} associate silicosis with the development of cor pulmonale, there are little supporting data available. The results of the regression analysis of this study show a clear gradient of odds ratios corresponding to the severity of silicosis from slight to extensive grades of the disease.

Mortality studies have shown a slight increase in deaths due to heart disease among miners exposed to silica but cor pulmonale was not a subject of these studies.^{15,16} Other studies^{17,19,20} of the relation between silicosis and cor pulmonale have been limited by virtue of the few cases and flawed by poor epidemiological and statistical methods. Methods of assessing right ventricular hypertrophy have not been reliable. The only accurate method for assessing right ventricular hypertrophy^{1,21} requires dissection of the heart according to Fulton's technique,⁹ a time consuming procedure that is rarely undertaken.

The data presented also show an association between emphysema and cor pulmonale. Marked emphysema was present in 9.2% of cases and 0.6% of controls (table 4) with an OR of 21.32 ($p = 0.0011$) and moderate emphysema in 44% of cases and 24.6% controls (OR 2.77, $p = 0.0011$). Studies concerning the association between emphysema and cor pulmonale in the general population have given conflicting results. Some investigations have implicated the extent²² or the type^{23,24} of emphysema in the development of cor pulmonale whereas other studies^{25,26} have failed to confirm a relation between emphysema and cor pulmonale.

In gold miners, emphysema occurs independent of pneumoconiotic changes. Several epidemiological studies have shown that exposure to silica dust, independent of the presence or severity of silicosis, is a risk factor for the development of emphysema.²⁰⁻²⁸ The risk of developing emphysema is more strongly associated with cigarette smoking than with exposure to dust; exposure to silica dust, in the absence of cigarette smoking, is associated only with insignificant and not moderate or marked emphysema.²⁸ It is likely that exposure to dust plays a part in the development of cor pulmonale. Detailed information was unfortunately not available for this study and the causative role of exposure to dust will have to be considered in another study.

POTENTIAL SOURCES OF BIAS

Pack-years of smoking history were unavailable and subjects were crudely grouped according to smoking state, which was also unavailable for 20.5% of the study population.

The presence of cor pulmonale in some subjects with only insignificant emphysema as well as in subjects without silicosis suggests that airways dis-

ease (chronic bronchitis and bronchiolitis) may also play a part. Numerous reports have documented the importance of peripheral airway narrowing in the development of right ventricular hypertrophy.^{2,3,25} These data, however, were unavailable for this study.

Ischaemic heart disease is so prevalent that using it as an exclusion criterion would have resulted in an inadequate number of subjects for analysis. The proportion of cases with ischaemic heart disease was, however, similar to that of controls.

In conclusion, this study has provided evidence for the association of silicosis with the development of cor pulmonale, a theory that has lacked substantiating evidence in previous studies. Not only has the presence of silicosis been shown to be a risk factor for cor pulmonale in gold miners, but the risk increases with the severity of silicosis (from slight to extensive disease).

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