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The impact of pleurodesis in malignant effusion on respiratory function

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Pleurodesis of malignant pleural effusion provides for a substantially better quality of life compared to onging exudation with the need for repeated evacuation of fluid. Successful pleurodesis leads to permanent cessation of fluid production as a result of the formation of fibrous adhesion between the lung and costal pleura which in theory, however, might restrict lung mobility. In patients with poor lung function, or with need for bilateral pleurodesis, the apprehension of further impairment of lung function often arises. The aim of this study was to evaluate the effects of pleurodesis on lung function. Therefore 10 patients with malignant pleurisy with very limited tumour were investigated. They were without radiological signs of tumour infiltration in the lung parenchyma, without visible tumour growth in the pleural space during thoracoscopy and had undergone a successful one-sided pleurodesis. Respiratory function tests were performed at different times, 1–102 months after pleurodesis. The assessment consisted of: static and dynamic spirometry, exercise testing with blood gas determination and radiospirometry.

Spirometric values were slightly low, but in general within the reference limits. Blood gas determination showed no signs of alveolar hypoventilation. Radiospirometry showed a slight attenuation of activity in the treated lung but similar turnover of gas of the treated *vs.* the untreated side. The study showed that pleurodesis in malignant pleurisy has only minor impact on respiratory function.

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Introduction

Metastatic or direct spread of malignant tumours to the pleura may cause recurrent large pleural exudates, prompting repeated thoracocenteses. The most common primary tumours are lung and breast carcinoma (1). The first measure in a substantial malignant pleural effusion is thoracocentesis, which gives temporary relief of symptoms. However, recurrent thoracocenteses lead to a risk of fibrin and/or malignant cells covering the lung surface, thereby restricting expansion of the lung (2), cause loss of protein and blood cells and also constitute an unpleasant and terrifying reminder of the disease, in addition to the cost of the medical care. Thus, if thoracocentesis has to be repeated, pleurodesis is indicated. Successful treatment leads to permanent inhibition of fluid production with minor pleural thickening, relief of dyspnoea, cough and psychological relief. Many agents have been used to achieve pleurodesis. Currently the most commonly used agent seems to be sterilized talc (3). However, in many European centres, including ours, atabrine (Quinacrine, Vipor Chemical, Baroda, Italy) has been used with good results and minor side effects for at least 20 yr (4–7). Pleurodesis is achieved by an inflammation, causing fibrotic reaction and adhesion of the pleurae (1,8). The influence of the procedure on lung function in malignant pleural disease is difficult to evaluate. Long-term follow-up is rarely possible because of the progressive nature of the underlying disease. The aim of this study was to evaluate the effects of pleurodesis *per se* on lung function measured by dynamic and static spirometry, blood gases at rest and during exercise and by ventilation/perfusion scintigraphy.

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Methods

The criteria for inclusion in the study were: 1) Recurrent one-sided malignant pleurisy, 2) no signs of tumour growth or bulk in the lung parenchyma on chest radiography at the time of admission nor at the time of functional assessment, 3) no visible tumour growth in the pleural space on thoracoscopy, 4) successful pleurodesis (diminishing of pleural fluid production to less than 50 ml 24 h^{-1} before chest tube removal and no signs of recurrence with need for further evacuation of fluid), 5) a uniform circumferential thickening of the pleura as determined with computerized tomography of less than 1 cm so as to optimize the conditions for radiospirometry and 6) informed consent by the patient.

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PATIENTS

The case histories of all patients who had undergone thoracoscopy because of recurrent effusion from January 1986 and June 1996 were scrutinized. Out of a total of 733 cases, 10 patients were in relatively good health and fulfilled the criteria for inclusion and were able and willing to participate in the study.

There were three males and seven females, mean age 66 ± 13 years (range 42–85 years). The time from pleurodesis to functional assessment varied from 1–102 months with a median of 12 months. The sites of primary tumour were the breast in four (patients no. 2,4,6 and 7), the lung in two (patients no. 8 and 9), both small cell lung carcinoma, one patient had a mesothelioma (patient no. 3), and one each from the following organs: ventricle (patient no. 5), lymph nodes (patient no.1, Mb Hodgkin) and ovary (patient no.10). There were five smokers, three ex-smokers and two patients who had never smoked. None of the patients had clinical signs of extrapulmonary ventilatory impairment, or a past history of chronic bronchitis or asthma. The study was approved by the local ethics committee and the isotope committee.

THE PROCEDURE OF PLEURODESIS

The procedure of pleurodesis has been previously described (4–7). After thoracoscopy, a drainage tube of 20 mm was inserted between the ribs and when the lung had expanded on chest radiography, 600 mg of Quinacrine dispersed in 20 ml saline was instilled intrapleurally. The chest tube was removed when the fluid production was less than 50 ml $24\ h^{-1}$. This procedure lasted 4–7 days.

FUNCTIONAL TESTS

Patients were investigated 1–102 months after pleurodesis, when judged to be in good general health and the underlying malignancy was under control.

1. *Spirometry:* Static and dynamic spirometry were performed using a Pulmonary Function 2400 spirometer (Sensor Medics, Bilthoven, The Netherlands) connected to an IBM Computer 486 DX2/SP. The static lung volumes, i.e. total lung capacity (TLC) and residual volume (RV), were determined with helium dilution. Slow and forced vital capacity (VC and FVC) and the forced expired volume in 1 sec ($FEV_{1.0}$) were measured and the percentage of FEV_1/VC (FEV%) was calculated. Flow-volume curves were plotted from the best of three forced expirations. The maximal voluntary ventilation was determined at a respiratory rate of 40 min^{-1} (MVV_{40}). Reference values according to the European Coal and Steel Community were used (9).

2. *Exercise test:* Patients exercised sitting on a bicycle ergometer, starting at a work load of 30 W which was increased by 10 W every minute to a symptom limited maximum. Chest pain, dyspnoea and leg fatigue were assessed according to Borg's scale (10).

3. *Blood gases at rest and exercise:* Arterial blood samples were withdrawn from an indwelling short plastic cannula in the radial artery, for determination of arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), pH and arterial oxygen saturation (SaO_2). Samples were anti-coagulated with heparin sodium and analysed immediately. PaO_2, SaO_2, $PaCO_2$ and pH were measured with a blood gas analyser (IL BGM 312, Instrumentation Laboratories Inc., Lexington, U.S.A). A sample was taken at rest, at maximal work load and 10 min after exercise. In one patient it was not possible to insert the arterial cannula. SaO_2 was then measured with a pulse oximeter (Nellcor Inc., Hayward, Ca., U.S.A.)

REGIONAL LUNG FUNCTION

Regional lung function was measured using the method of radiospirometry (11). Lung perfusion was imaged following intravenous injection of 74 MBq 99m-technecium (^{99m}Tc) macroaggregated albumin. A dorsal image of the distribution was acquired on a gamma-camera system (Gamma-camera: SX300, Picker International, Cleveland, Ohio, U.S.A.; PDP11/73 Gamma 11 computer: Nuclear Diagnostics, Stockholm, Sweden). Without changing the position of the patient with respect to the gamma-camera, the patient then breathed into a closed spirometer and a bolus of 1000 MBq 133-Xenon (^{133}Xe) gas was introduced into the inhalation side of the spirometer. Images were acquired for 30 sec from the start of inhalation. Approximately 5 min later, when ^{133}Xe had equilibrated in the lungs, the spirometer was opened to the air and ^{133}Xe gradually 'washed-out' from the system at a rate depending on tidal volume and degree of gas retention in the lungs. Images were acquired for 5 min from the start of wash-out.

All ^{133}Xe images were corrected for down scatter from ^{99m}Tc in the ^{133}Xe energy window and for activity in the chest wall (background). An image representing regional ventilation was generated by adding the images from the start of ^{133}Xe inhalation to give a total of 300 000 counts. From the perfusion image data, the total counts in each lung were summed and expressed as a percentage of the total counts in both lungs (relative perfusion $\dot{Q}$). Relative ventilation ($\dot{V}$%) for each lung was calculated in a similar manner from the ventilation image data. The values obtained were then used to calculate a $\dot{V}/\dot{Q}$ ratio for each lung. The time ($T_{1/2}$) taken for half the ^{133}Xe gas present at the start of wash-out, to disappear from each lung was also calculated. $T_{1/2}$ was calculated from the area (A) below the wash-out curve and its initial height (H) according to the formula $\ln 2 \times A/H$.

STATISTICAL ANALYSIS

Group data are expressed as means ± 1 standard deviation unless otherwise stated. The Mann–Whitney *U*-test for unpaired observations was used for comparison of ventilation/perfusion ratios and turn-over of gas between treated and untreated lungs.

TABLE 1. Spirometric values in 10 patients 1–102 months after succesful one-side pleurodesis [Percentage of predicted values (Mean ± SD)]

Patient number	TLC%	RV%	VC%	FVC%	FEV_1%	FEV%	MVV_{40}%
1	82	89	82	84	83	101	82
2	84	87	87	80	67	80	69
3	91	72	112	108	104	92	82
4	80	87	80	81	69	90	66
5			101	107	88	92	68
6	98	99	102	98	82	80	77
7			82	74	77	72	68
8	81	91	80	79	76	93	70
9	132	185	101	106	87	89	71
10	124	148	115	114	104	95	107
Total	8	8	10	10	10	10	10
Mean	96·5	107·25	94·2	93·1	83·7	88·4	76
SD	20·45	38·61	13·56	14·93	12·72	8·58	12·35

For abbreviations see text.

Results

SPIROMETRY

Most of the values for volume and flow were between 80–90% of predicted values when adjusted for age and gender of the patients (Table 1). Three patients (patients no. 4, 7 and 8) underwent lung function test 5–6 weeks after pleurodesis. Their spirometric values tended to be slightly lower compared to the patients who performed the lung function test many months to years after pleurodesis. Two patients (patients no. 5 and 7) did not perform static spirometry. Their vital capacities were within the normal range. Their FEV_1/VC (FEV %) were 92% and 72 % of predicted, respectively.

EXERCISE TEST

The patients managed from 60 W to 150 W on the bicycle with a mean of 95 ± 26 W. The majority of the patients stopped exercising because of dyspnoea and/or leg fatigue.

BLOOD GASES

PaO_2 and $PaCO_2$ at rest were within normal limits 11·1 ± 1·4 kPa and 4·9 ± 0·3 kPa respectively. Mean SaO_2 was 96·7 ± 1·4 %. During and after exercise. PaO_2 increased normally and conversely, $PaCO_2$ tended to decrease (Fig.1).

RADIOSPIROMETRY

There were slight reductions of activity in the treated lungs, both in the perfusion and ventilation studies. However, when ventilation/perfusion ratios were calculated there was no significant difference between the lungs (Table 2). The turn over of xenon for each lung was expressed in terms of the wash-out curves obtained at radiospirometry. The wash-out ($T_{1/2}$) did not differ significantly between the treated and untreated lungs (Fig. 2). Data from nine patients were used in the analysis because one patient (patient no. 7) was not able to complete the procedure.

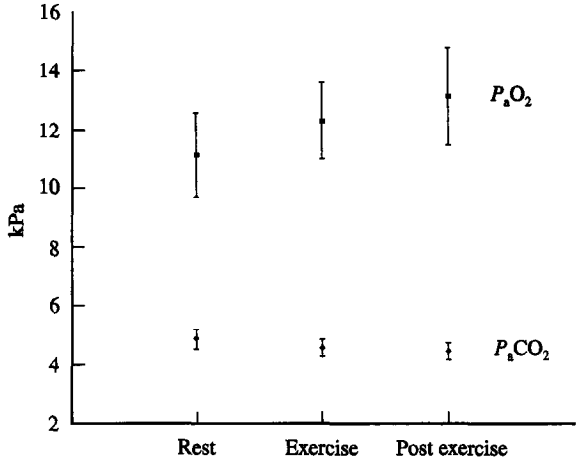

FIG 1. Blood gases at rest, during and 10 min after excercise in 9 patients after successful one-sided pleurodesis. Mean ± SD

Discussion

The main observation of this study was that pleurodesis *per se* in malignant pleurisy without visible tumour in the lung parenchyma and in the pleural space has only a minor limiting influence on gas turn-over of the affected lung and on the total respiratory function. Viskum *et al.* reported a similar result after talc pleurodesis for spontaneous pneumothorax (12), confirming a previous report by

TABLE 2. Relative distribution of perfusion, ventilation and volume in 9 patients after a succesful one-sided pleurodesis.

Patient number	Treated side	$\dot{Q}$%L	$\dot{Q}$%R	$\dot{V}$%L	$\dot{V}$%R	V%L	V%R	$\dot{V}/\dot{Q}_t$	$\dot{V}/\dot{Q}_u$
1	Left	34	66	41	59	43	57	1·21	0·89
2	Left	30	70	37	63	44	56	1·23	0·90
3	Left	45	55	48	52	45	55	1·07	0·95
4	Left	22	78	19	81	20	80	0·86	1·04
5	Right	48	52	53	47	49	51	0·90	1·10
6	Right	50	50	45	55	47	53	1·10	0·90
7	Right								
8	Right	79	21	76	24	64	36	1·14	0·96
9	Right	49	51	35	65	41	59	1·28	0·71
10	Left	43	57	39	61	40	60	0·91	1·07
	Mean	44·44	55·56	43·67	56·33	43·67	56·33	1·08	0·95
	SD	16·13	16·13	15·45	15·45	11·38	11·38	0·16	0·12

The ventilation/perfusion ratios for the treated (t) and untreated (u) sides are given (Mean ± SD, $\dot{V}$: ventilation; V: volume; Q: perfusion; L: left; R: right

Knowles *et al.* (13). Otherwise, the literature on this subject is extremely limited. In our study, ventilation/perfusion ratios and gas turnover were similar in the treated and untreated lungs.

All patients with malignant effusion without response to systemic cytostatic and/or endocrine treatment, should if possible undergo pleurodesis, because pleurodesis provides for a substantially better quality of life compared to ongoing exudation with need for repeated evacuation of fluid. Pleural diseases may lead to restrictive ventilation impairment. Minimal pleural thickening can cause a reduction in unilateral ventilation that may not be compensated for by the contralateral lung (14). In cases of pleuropneumonia and empyema, one of the objectives with immediate treatment is to control infection, thereby minimizing progressive pleural thickening and pleural restriction in order to counteract reduction of the lung volume and conserve respiratory function. It would have been of interest to compare our results with that of patients who had been treated for empyema for example, but no such control group could be established and we are not aware of any such study.

The number of patients in the present study was small. Out of 733 patients with large effusions only 10 finally met the strict inclusion criteria. Functional assessments were performed 1–102 months after pleurodesis because seven patients had undergone pleurodesis long before the study was initiated. Of the four patients with breast carcinoma, three had received postoperative radiotherapy towards the chest wall. The only patient with Morbus Hodgkin (no. 1) was treated with chemotherapy and Mantel radiotherapy. Previous observations have shown that local and/or loco-regional radiotherapy to the chest wall impairs lung function (15,16), but the results obtained in our patients did not show strikingly abnormal values. This may be partly due to the relatively long duration between radiation

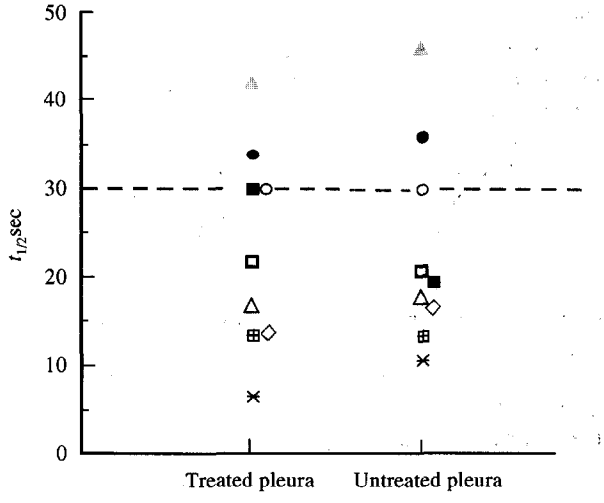

FIG 2. Washout time ($T_{1/2}$) for xenon in 9 patients after successful one-sided pleurodesis. Each patient is represented with identical symbols for the treated/untreated pleura. The dotted line represents the highest normal value.

and pleurodesis and the functional tests. Thus any underlying acute inflammatory process in the lung parenchyma and the pleura would have subsided. Two of the patients (no. 5 and no. 7) only performed dynamic spirometry, hence the missing values for residual volume (RV) and total lung capacity (TLC). However, their vital capacities (VC) of 101 and 82% of predicted respectively did not indicate a restrictive ventilation impairment.

The two parameters used to describe lung function by radiospirometry were ventilation/perfusion ($\dot{V}/\dot{Q}$) ratios and the wash-out time for 50% of Xenon gas from the lung,

($T_{1/2}$). The $\dot{V}/\dot{Q}$ ratio indicates how well ventilation and perfusion are matched within the lungs, a value of $1{\cdot}1 \pm 0{\cdot}1$ indicating normal lung function (11). The wash-out time is a measure of gas turnover in the lungs. A value for $T_{1/2}$ less than 30 sec is considered normal and longer time indicates an increasing degree of obstructive and restrictive lung disease (11). In two patients (patients no. 1 and 5), the wash-out times were slightly above the normal limit (30 sec) for both of their lungs. Patient no. 1 was an ex-smoker and patient no. 5 was a smoker. Assessment of regional lung function in patients with pleural disease can be complicated by the presence of a non-uniform thickening of the pleura. Emission from all radioisotopes is attenuated in tissue. For ^{99m}Tc and ^{33}Xe the attenuations are approximately $12\%cm^{-1}$ (12% per cm) and $16\%cm^{-1}$ (16% per cm), respectively (17,18). When regional differences in distribution are expressed as a percentage of the total activity registered, activity in the treated lung will be underestimated in proportion to the pleural thickening. Since pleural thickness could not be estimated more than semi-quantitatively by the CT-scan, only a crude correction could be made for tissue attenuation and consequently the differences observed between the treated and untreated lungs in terms of percentage uptake were less than precise. The results expressed in terms of $\dot{V}/\dot{Q}$ and wash-out times are to a large extent independent of attenuation and, therefore, a better method for comparing function in the treated and untreated lungs.

The adequate increase in arterial oxygen tension during and after exercise, without signs of alveolar hypoventilation further corroborates that neither any significant ventilation/perfusion imbalance nor any major diffusion limitations were at hand.

To the best of our knowledge, there are no previous studies on the influence of pleurodesis on respiratory function in malignant disease, illustrating that pleural effusion is often (except in cases of mesothelioma) a late manifestation with poor prognosis, even when effusion is the first sign of malignancy.

Conclusion

In conclusion, this study shows that successful pleurodesis does not compromise the lung function.

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