Thorax 1990;45:509–513

Bronchoscopic cryotherapy for advanced bronchial carcinoma

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Abstract

A prospective study was carried out to assess the value of bronchoscopic cryotherapy for palliation of inoperable bronchial carcinoma with bronchial obstruction. Symptoms, lung function, and chest radiographic and bronchoscopic findings were recorded serially before and after 81 cryotherapy sessions in 33 consecutive patients. Most patients improved in terms of overall symptoms, stridor, and haemoptysis and they had an overall improvement in dyspnoea. Objective improvement in lung function was seen in 58% of patients and the changes in lung function correlated with symptoms. Bronchoscopic evidence of relief of bronchial obstruction was seen in 77% of patients and 24% showed improvement in degree of collapse on the radiograph. There were no important complications. These results compare favourably with the results in published series of patients having laser therapy. It is concluded that bronchoscopic cryotherapy is valuable for the palliation of inoperable bronchial carcinoma.

Endobronchial obstruction is an important cause of morbidity in advanced bronchial carcinoma. Radiotherapy may be very effective in reducing tumour size but its benefit may be temporary, and further treatment is limited by the total dose that can be given. Recent interest has focused on laser therapy as a local method of clearing such obstructions, though this treatment may be associated with appreciable morbidity and mortality.[1–8] Bronchoscopic cryotherapy has been used in endobronchial malignancy.[9–13] Retrospective studies have suggested that bronchoscopic cryotherapy may offer substantial palliation of dyspnoea, stridor, and haemoptysis in patients who have failed to respond to other treatments, or who cannot have other treatment. We aimed to assess the possible benefits of cryotherapy by means of a prospective study of symptoms, chest radiographs, lung function, and bronchoscopic findings before and after treatment.

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Accepted 4 April 1990

Methods

Patients with malignant endobronchial lesions were accepted for cryotherapy if referred with predominant symptoms attributable to endobronchial obstruction. All such patients who received cryotherapy for the first time at Harefield Hospital during October 1988–May 1989 were included in the study. Each patient was assessed clinically and had chest radiography and lung function tests shortly before the first treatment whenever possible. Subsequent assessments were made two to four weeks after each treatment, or immediately before the next treatment if this was earlier. Patients usually received three cryotherapy treatments, with a two week interval between the first and the second treatment and four weeks between the second and the third. Additional treatments were given as indicated clinically, but the data in this report refer only to the first three treatments in each patient. Occasionally the severity of a symptom such as stridor or the presence of a carinal lesion causing substantial obstruction of both main bronchi necessitated a reduction in the interval between treatments to a minimum of one week. All lesions were judged to be inoperable because of an unfavourable site, regional spread, distant metastases, or the patient's poor general health or respiratory state.

CLINICAL ASSESSMENT

Clinical assessment included grading of the symptoms experienced in the week preceding the assessment. *Dyspnoea* was graded from 0 to 3 according to a modification of the Medical Research Council dyspnoea index[14]: 0—ability to hurry up a hill or up stairs; 1—unable to hurry, but able to maintain a normal walking pace on the level for more than six minutes; 2—unable to maintain a normal walking pace on the level for more than six minutes without stopping; 3—short of breath at rest or on minimal exertion such as dressing or undressing. *Haemoptysis* was graded from 0 to 4: 0—no haemoptysis; 1—streaks of blood in the sputum; 2—clots of blood on 4 days or less during the preceding two weeks; 3—clots on 5 or more days; 4—haemoptysis requiring blood transfusion. *Cough* was graded 0 to 2: 0—no cough; 1—cough not disturbing sleep; 2—cough disturbing sleep. Patients were asked whether overall they felt better, the same, or worse than before their last treatment. *Stridor*, recorded as present or absent, was defined as inspiratory wheeze associated with loud or noisy breathing heard at the mouth with the unaided ear. The inspiratory wheeze was elicited on forced inspiration if not elicited during normal breathing.

Plain posteroanterior chest radiographs were obtained at each assessment before treatment and compared with the film from the preceding assessment.

LUNG FUNCTION TESTS

Whenever possible forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and maximum expiratory and inspiratory flow rates (MEF, MIF) were recorded from a single forced expiratory and inspiratory deep breath with the Microloop turbine spirometer (MicroMedical company). After three satisfactory manoeuvres the measurements recorded were from the one that gave the highest values for FVC and FEV_1. Many patients found it difficult to perform a full expiratory and a full inspiratory manoeuvre in one breath; measurements of MIF showed poor reproducibility and were probably submaximal. For the last 28 assessments MIF was recorded as the best of three separate inspiratory manoeuvres; only these data are given. Predicted values of FVC, FEV_1, MEF, and MIF were obtained.[15]

A six minute walk test was performed at each assessment whenever possible.[16] Arterial blood gases with the patient breathing air at rest were measured initially at the first and fourth assessments, but were attempted at all assessments in the last 17 patients.

The airway response to 2·5 mg nebulised salbutamol was measured at the first assessment, and at subsequent assessments if the patient showed an improvement initially of 15% in FEV_1 or FVC after salbutamol, with an absolute improvement of at least 0·2 (FEV_1) or 0·3 (FVC) l.[17] An increase in MEF or PIF of 20% of the baseline value, in arterial oxygen tension (Pao_2) of 1 kPa, or in six minute walk distance of 50 m or a reduction in symptom score of one unit was considered to be an improvement.

CRYOTHERAPY

Cryotherapy was performed under general anaesthesia through a rigid bronchoscope as described.[11] The endobronchial lesion was frozen by applying a bronchial cryoprobe tip and cooled to a minimum of −70°C with circulating liquid nitrous oxide. The probe was allowed to thaw and then the lesion was refrozen. Continuous suction recovered blood and secretions from the site during the procedure. The entire procedure took about 10–15 minutes. The degree of bronchial obstruction was estimated before cryotherapy at each site in terms of percentage occluded (from 0%—completely patent—to 100%—completely occluded), and whether or not there appeared to be an extrabronchial component to the bronchial narrowing was recorded.

Data from individual patients before and after cryotherapy were compared by means of Student's paired *t* test. The relation between changes in various measurements with treatment were assessed by correlation coefficient.

Results

Thirty three patients (23 male) with bronchial obstruction due to malignant endobronchial tumour received cryotherapy for the first time during the study period. Details of patients and tumours are presented in tables 1 and 2. Patients were generally old and frail; 14 (42%) were aged over 75 (range 48–89) years. No patient was refused treatment with cryotherapy if the predominant symptom was thought to be related to endobronchial obstruction and other treatment was not possible. Ten patients had received radiotherapy before being considered for cryotherapy. One patient who had had a left pneumonectomy four years previously received cryotherapy for an endobronchial malignant lesion of the right main bronchus.

All but one patient reported breathlessness as the predominant symptom before treatment. Twelve patients were breathless on minimal exertion. Almost all patients had radiographic evidence of collapse of at least one lobe. Seven patients had stridor and nine haemoptysis. Thirty patients reported cough, which disturbed sleep in five cases.

All patients had been smokers and most had flow-volume curves suggesting chronic airflow limitation. Twelve patients had an improvement in their airflow limitation after inhaling salbutamol.

Cryotherapy was performed on 81 occasions in the 33 patients. Nineteen patients had treat-

Table 1 Details of patients before cryotherapy

	n	*Mean*	*SD*
Age (y)	33	71	9
FEV_1 (% pred)	33	57	18
FVC (% pred)	33	76	21
FEV_1/FVC (%)	33	60	11
MEF (% pred)	33	42	19
MIF (% pred)	11	49	17
6 min walk distance (m)	27	328	137
Pao_2 (kPa)	27	9·8	1·3
Dyspnoea index	33	1·8	1·0

FEV_1—forced expiratory volume in one second; FVC—forced vital capacity; MEF—maximal expiratory flow; MIF—maximal inspiratory flow; Pao_2—arterial oxygen tension.

Table 2 Tumour details

	No (%) of patients
Site (48 sites in 33 patients)	
Trachea	2 (4)
Left main bronchus	9 (19)
Right main and intermediate bronchus	14 (29)
Lobar bronchi	23 (48)
Patients with extrabronchial component noted at first bronchoscopy	14 (42)
Chest radiograph	
Collapse of one or more lobes	29 (88)
Histological type	
Squamous cell carcinoma	25 (76)
Undifferentiated cell carcinoma	
Large cell	6 (18)
Small cell	1 (3)
Malignant spindle cell tumour	1 (3)
Metastatic disease	
Cervical lymphadenopathy	3 (9)
Serum alkaline phosphatase >150% upper limit of normal	8 (24)
Serum adjusted calcium >2·7 mmol/l	5 (15)

Table 3 Numbers and percentages of patients showing improvement from baseline at the final assessment after cryotherapy*

	n†	No (%) improved
Dyspnoea score	27	10 (37)
Haemoptysis	9	6 (67)
Stridor	7	4 (56)
Radiographic collapse	29	7 (24)
FEV_1	29	7 (24)
FVC	29	7 (24)
MEF	29	6 (21)
PIF	11	3 (27)
Pao_2	21	7 (33)
6 min walk	22	6 (27)
Endobronchial obstruction	26	20 (77)

*See text for definition of improvement.
†Number of patients assessed before and after cryotherapy; for symptoms numbers include only those patients with a score ≥ 1 at baseline.
For abbreviations see table 1.

ments on three occasions. Reasons for withdrawal before the third treatment were death from progressive disease (seven cases), development of cerebral metastases (three cases), and general deterioration despite treatment (two cases). Two patients had a single treatment with cryotherapy for immediate relief of symptoms before referral for radiotherapy.

Twenty three patients (70%) reported overall subjective improvement after cryotherapy. A further three patients improved initially but subsequently deteriorated. The number of patients with improvement in symptom scores and lung function following cryotherapy is shown in table 3.

Relief of dyspnoea was the most common benefit from treatment, the mean improvement in dyspnoea score between the first and the last assessment being 0·5 ($p < 0·02$). Stridor had resolved completely in four patients by their last assessment but it persisted or recurred in three patients. Four patients had complete resolution of haemoptysis, two after the first treatment and two after the third. In a further two patients haemoptysis improved. Cryotherapy had no effect on cough overall and changes in cough score tended not to be sustained.

According to the radiographic evidence, collapse resolved completely in two of the 23 patients and diminished in a further five.

Nineteen patients showed improvement in at least one objective measurement of lung function, and eight improved in more than one; in seven patients the improvement was in FEV_1. Change in FEV_1 correlated with change in dyspnoea score ($r = 0·47$, $p < 0·02$; fig 1) and change in resting arterial oxygen tension correlated with change in the six minute walk test ($r = 0·67$, $p = 0·005$; fig 2).

After a single application of cryotherapy the mean improvement in estimated bronchial patency at each site was 22% of the predicted normal calibre ($p < 0·001$). In the 14 patients assessed by bronchoscopy four weeks after a second treatment there was a further mean improvement of 20% of the predicted normal calibre per site ($p = 0·05$).

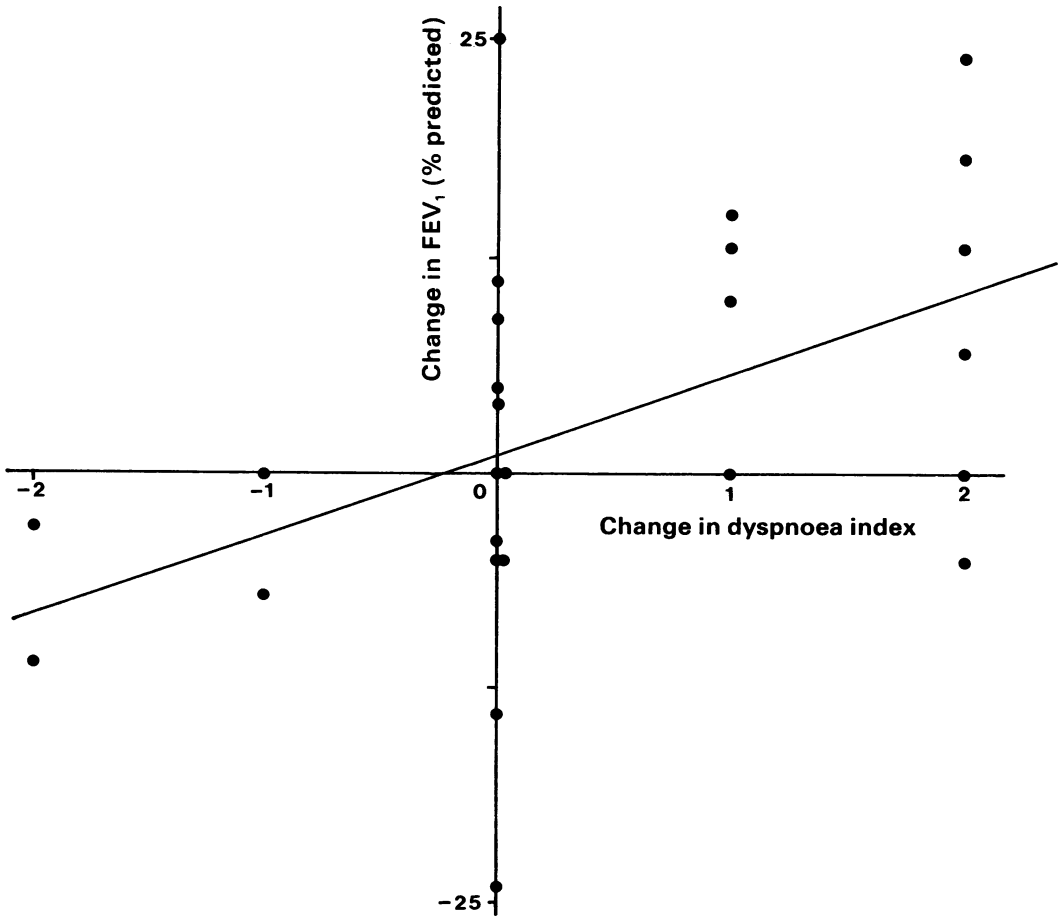

Figure 1 Relation between changes in FEV_1 and dyspnoea score from baseline to after last cryotherapy treatment ($r = 0·47$, $p < 0·02$) (positive values represent improvement).

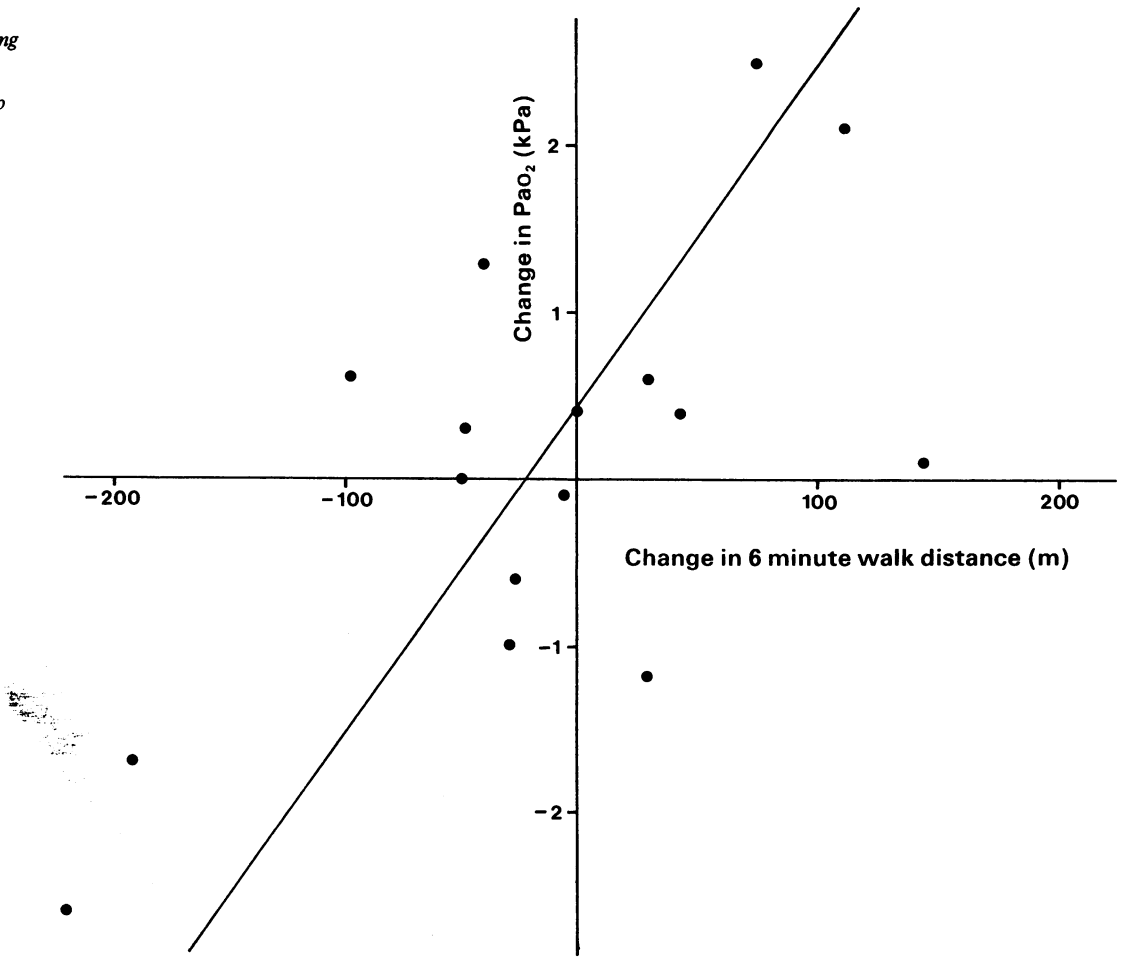

Figure 2 Relation between changes in resting arterial oxygen tension and six minute walk distance from baseline to after last cryotherapy treatment ($r = 0{\cdot}67$, $p = 0{\cdot}005$) (positive values represent improvement).

Some patients expectorated small amounts of blood stained sputum and necrotic material for a few days after cryotherapy. There was no appreciable haemorrhage or infection and no pneumothoraces after cryotherapy. No patient required intubation or mechanical ventilation after the procedure.

Discussion

Bronchoscopic cryotherapy for endobronchial malignancy was first described in man by Sanderson *et al.*[9] Most reports so far have been retrospective and measures of improvement have tended to be qualitative rather than quantitative. Our results are broadly similar to those of others, however.[11-13]

Our patients were generally old and frail and severely limited by breathlessness, and many had experienced stridor and haemoptysis. All had inoperable tumours and alternative treatments generally either had failed to control symptoms or were not possible because of the patient's general condition. The aim of any intervention in such patients is palliative, and the expected course without treatment would be progressive deterioration. Our results should be viewed against this background.

Although only the improvement in dyspnoea score and bronchial patency were statistically significant for the group as a whole, many patients had greater improvements in lung function, chest radiographs, or exercise tolerance than would be expected from the variability inherent in the techniques of measurement. That such changes are of physiological importance is supported by the significant correlations between changes in lung function, symptoms, and exercise capacity (figs 1 and 2).

The low incidence of complications in this study reflects our previous experience with cryotherapy.[11] The low incidence of anaesthetic problems, even though many patients were elderly and hypoxaemic, with pre-existing chronic lung disease and malignant bronchial obstruction, is probably due to the short duration of general anaesthesia and the anaesthetic expertise. All cryotherapy procedures were carried out by a single experienced operator (MOM).

It is not usually possible to effect complete bronchial clearance with a single application of cryotherapy. Attempts at more complete bronchial clearance with a single treatment may increase the risks of arterial perforation and pneumothorax. Although patients often observe symptomatic benefit after a first treatment, additional benefit is frequently observed after a second or third treatment. Inpatient stay and convalescence from the procedure are usually brief. Most patients are admitted on the morning of the treatment and discharged home the following day; several have been successfully treated as day cases. A palliative procedure such as cryotherapy should have a

minimum of adverse effects and result in the minimum time away from home and family.

Other treatments have been proposed for malignant endobronchial obstructions, including laser therapy,[1-8] photodynamic therapy,[18] and endobronchial radiotherapy.[19] Of these, laser therapy has been most extensively investigated. Gelb and Epstein used spirometry and a modified Medical Research Council dyspnoea index to assess response to laser treatment in 19 patients with complete bronchial obstruction, with results similar to our own.[8] Improvement in haemoptysis is observed in around two thirds of patients after laser therapy,[1 2] as after cryotherapy in our experience. Reduction of radiographic collapse may be expected in 22–39% of cases after laser therapy[1-4] (24% after cryotherapy in our study). Improvement in arterial oxygenation may be seen in one third of patients after either laser therapy[2] or cryotherapy. When the airway is completely obstructed at bronchoscopy 58% of sites were relieved by laser therapy,[2] compared with 61% in our study.

Laser therapy, however, is associated with several important complications. Appreciable haemorrhage is reported in 0·2–10% of laser treatments, and may be fatal.[5-7] Pneumothorax is reported in around 1% of laser treatments.[6 7] Effective bronchial clearance may be attained with a single laser treatment but may require one to two hours of general anaesthesia and prolonged mechanical ventilation may be necessary afterwards.[2]

Although our results with cryotherapy compare favourably with published reports of laser therapy, comparative trials have not yet been performed. Outcome will also depend on the experience of the operator and anaesthetic staff, the condition of the patient, and the nature of the tumour. A double blind study would be difficult to achieve and the use of objective measures of palliation is essential. In our study endobronchial patency did not correlate well with other measures of outcome, possibly because of the difficulty of assessing the condition of lung and airways distal to the malignant obstruction. We found symptom scores, lung function measurements, and radiographs useful additions to endobronchial assessment in evaluating responses to treatment.

We have found that bronchoscopic cryotherapy provides useful palliation of dyspnoea, stridor, and haemoptysis in bronchial obstruction due to predominantly endobronchial malignancies, and that it has a low risk of adverse effects.

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