The role of cryotherapy for airway complications after lung and heart–lung transplantation

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Abstract

Objective: Although airway problems after lung and heart–lung transplantation have been greatly reduced due to changes in surgical technique, excessive granulation tissue at the anastomosis may threaten airway patency. Treatment options include electrocautery, dilation, laser coagulation and stent placement however, recurrence remains a problem. Cryotherapy, the controlled application of extreme cold, is effective at causing cell lysis in granulation tissue and may therefore be effective after lung transplantation for airway problems arising from granulation stenosis. Our objective was to review our experience with cryotherapy as a first-line treatment for airways compromised by granulation tissue after lung and heart–lung transplantation.

Methods: A retrospective analysis of patient records after lung and heart–lung transplantation was performed. A total of 696 patients were identified who received lung or heart–lung transplants, 64 of whom were found to have granulation tissue at the site of airway anastomosis (8.9% of 721 airways at risk). When the granulation tissue was found to narrow the lumen by $\geq 50\%$ and affect lung function. Results: The trachea was involved in 5 patients and the main stem bronchus in 16. Each patient required a mean of 2.6 $\pm$ 2.0 Cryoapplications. Anatomical results of cryotherapy were judged excellent to good in 15 patients and fair in 6 patients. Eight patients required endobronchial stenting as part of a multimodality treatment. Overall, the post-treatment FEV$_1$ and FVC increased by 34 $\pm$ 36% and 25 $\pm$ 27% from pre-treatment values respectively ($P < 0.001$). In 13 patients in whom cryotherapy and dilation alone were effective, the FEV$_1$ increased by 41 $\pm$ 43% (range $-11$ to $138\%$) and the FVC by 28 $\pm$ 29% (range $-2$ to $96\%$). These changes were also significant ($P < 0.001$). Changes in these two parameters were positively and significantly correlated ($P < 0.01$). Actuarial survival at 3 and at 5 years were 57 and 43%, respectively (NS compared to total cohort), and median survival was 978 days (range 365–1862). Six patients are alive at a median follow-up of 5.75 years (range 0.6 to 8.3). Conclusions: We conclude that cryotherapy is a safe, effective treatment for excessive granulation tissue after lung and heart–lung transplantation and may reduce the need for endobronchial stenting and limit recurrence. © 1997 Elsevier Science B.V.

Keywords: Lung transplantation; Heart–lung transplantation; Cryotherapy tracheal; Bronchial complications; Granulation tissue

1. Introduction

Airway compromise secondary to stenosis at the site of tracheobronchial anastomosis is a relatively common event after lung and heart–lung transplantation. The incidence clinical intervention has been reported to be 7–9\% [1–3]. Ischaemia at the anastomotic site due to the relatively decreased vascularisation of the donor bronchial tree and the use of steroid therapy in immunosuppressive regimes has been the proposed mechanism of poor healing. Initial experience with airway anastomoses was discouraging
with significant morbidity and mortality secondary to stenosis and ischaemic dehiscence [4]. The progressive decrease in significant airway complications has resulted from both modifications of the procedure and the evolution of reliable means of treating these complications. The importance of leaving the peri-carinal and peri-bronchial tissue intact has resulted in better vascularised anastomoses [5]. En-block double lung transplantation has largely been supplanted by bilateral single lung transplantation with fewer airway complications in the bronchus to bronchus anastomoses than the tracheal anastomoses [4].

Other surgical techniques have been developed in an attempt to facilitate airway anastomotic healing. These have included wrapping the anastomoses in omentum, intercostal muscle or the internal mammary artery pedicle [6]; reanastomosis of the donor bronchial arteries to the recipient internal mammary arteries, and avoidance of excessive donor bronchus [4,5,7].

The successful treatment of post-transplant airway complication is often complex, prolonged, and requires experience with multimodality therapy. Intraluminal exuberant granulation tissue at the site of a healing ischaemic anastomosis continues to occur and may treated airway patency. After healing, varying degrees of fibrosis can result in stenosis. Thus a variety of therapeutic manipulations are often necessary. These have included electrocautery, laser coagulation, dilation and both silastic and metal stent placement [2,4,7–15]. Surgical treatment of retransplantation or sleeve resection has been a successful approach in severe bronchial stenoses [16].

Cryotherapy, the controlled application of extreme cold, was pioneered in 1986 for the pillation of bronchial carcinoma and subsequently has been used worldwide [17,18]. It is effective at causing cell lysis of granulation tissue as well. This is achieved by freezing the tissue to the temperature of −20°C or lower. This causes removal of pure water from the cells as intra- and extracellular ice crystals form and ultimately results in the rupture of cell membranes and cell death [19]. Tissue susceptibility is variable. Mucous membrane, from which granulation tissue arises, is cryosensitive whereas cartilage and connective tissues are relatively cryoresistant by comparison. If cryotherapy is applied during early tissue formation, before the development of fibrosis, the granulation tissue within the lumen is ablated without damage to the trachea or bronchial wall [20]. Our objective was to review the effectiveness of our experience with cryotherapy as the first-line treatment for airway compromise from granulation tissue after lung and heart–lung transplantation.

2. Materials and methods

There have been 696 patients who underwent lung and heart–lung transplants at Harefield Hospital from January 1986 to January 1996. All patients underwent routine bronchoscopic evaluation on post-operative days 7 and 10. Bronchscopy was performed subsequently as indicated by decreased pulmonary function studies at any time during follow-up. A total of 64 were found to have granulation tissue at the site of the airway anastomosis (8.9% of 721 airways at risk). In 21 patients the granulation tissue was found to decrease the lumen by ≥ 50% and affect lung function. The trachea was involved in 5 patients and the main stem bronchus in 16 (2.9% total airways at risk). There were 12 males and 9 females and the median age was 39.5 years (range 9–59). Cryotherapy was used as the initial treatment modality in 17 patients; 2 patients were treated for obstructing granulation tissue projecting between the interstices of a metal stent, and 2 patients were initially dilated for stenosis prior to the formation of granulation tissue.

The procedure was performed under general anaesthesia. A rigid Storz bronchoscope was used and oxygenation was maintained by Venturi positive pressure ventilation using a Sanders injector. All patients were biopsied prior to treatment. A Spembly 142 medical cryomachine using nitrous oxide as the cooling agent ensured a minimum temperature of −70°C at the cryoprobe tip. This was achieved via the Joule-Thompson effect of the nitrous oxide passing through a restricted nozzle within the chambers of the probe. A slightly angled 55 cm cryoprobe with a tip diameter of 3.5 mm was placed in direct contact with the granulation tissue. The probe was applied for 60 s, allowing a uniform ice ball to form. Complete thawing was then allowed prior to removal of the probe from the site to avoid trauma to the adjacent tissue caused by fracture of the ice ball from normal tissue. Continuous endobronchial suction through a long 3-mm external diameter catheter allowed removal of secretions and maintenance of good probe contact with the abnormal tissue. Procedure for stent insertion has been described previously [11,14].

Total procedure time was, on average, 20 min. Bronchoscopic reassessment was performed at 1–2 weeks. If incomplete ablation was noted, the procedure was repeated. Additional reassessment was performed in 2–4 weeks intervals until complete ablation was achieved. There was no evidence of tracheobronchial oedema. Only minor bleeding at the site of therapy was encountered. This was easily stopped using topical adrenalin in 1:1000 dilution in all cases.

Data are presented as medians and ranges or means ± S.D. Analysis of results pre- and post-cryotherapy has been achieved nonparametrically using...
Table 1
Demographic and clinical data on 21 patients undergoing cryotherapy for post-transplantation tracheobronchial stenosis arising from anastomotic granulation tissue

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Diag: 1, cryptogenic fibrosing alveolitis; 2, cystic fibrosis; 3, pulmonary fibrosis; 4, α1-antitrypsin deficiency; 5, emphysema; 6, primary pulmonary hypertension; 7, sarcoidosis.
Site: A, anastomosis; LUL, left upper lobe; RMB, right middle bronchus; RIB, right intermediate bronchus.
Nature: G, granulation tissue; S, slough; N, necrosis.
Onset and duration are days, follow-up is in years.
dFEV and dFVC are changes in pulmonary function parameters calculated as: [post-op value — pre-op value] litres; N/D—not done.
Surv?, indicates patients alive (Y) or decreased (N) at the time of writing.

the Wilcoxon paired signed ranks test, and with the Spearman rank correlation coefficient. Statistical significance at the 5% level has been adopted; all probabilities are two-tailed.

3. Results

Table 1 summarises the data obtained from the 21 patients. Ischaemia time was 269 ± 79 min (not significant against total cohort). Monofilament absorbable suture was used to sew the anastomosis in 20 patients and polypropylene in a single case; 9 patients underwent anastomotic revascularisation. Median onset of diagnosis of significant granulation stenosis was 85 days (range 24–387), and patients received a mean of 2.6 ± 2.0 applications. Anatomical results after completion of cryotherapy were judged good (constituting complete removal of tissue) in 15 patients and fair (residual tissue remaining) in 6. No cryotherapy-related complications or late recurrences of tissue were encountered. The number of patients who required endobronchial stenting after cryotherapy and dilation treatments was 8. Repeated treatments were used followed by bronchial dilation to allow the luminal diameter to be enlarged to facilitate the insertion of the stent. Repeated cryotherapy treatments resulted in maturation of the granulation tissue with resultant fibrosis. This facilitated airway stability after stent placement; 2 patients developed granulation tissue between the interstices of the metallic stents. Cryotherapy was also used to treat successfully this condition.

Both FEV1 and FVC increased significantly after the multimodality treatment (34 ± 36% and 25 ± 27% from pre-treatment values respectively; Wilcoxon paired signed ranks test P < 0.001 for both variables). For 13 patients for whom cryotherapy and dilation alone were effective, these parameters were similarly elevated (P < 0.001). The changes in FEV1 and FVC were positively and significantly correlated (Spearman P < 0.01).

The median duration of multimodality therapy was 76 days (range: 1–935) and the time to diagnosis of obstructive granulation tissue after transplant was unrelated to the subsequent resistance to therapy, or to the need for multimodality therapy. The Kaplan-Meier survival estimate for the cohort (+ 95% confidence limits) was 978 days (range 365–1862), and actuarial survival at 3 and 5 years was 57 and 43%, respectively. At a median follow-up of 5.75 years (range 0.6–8.3) 6 patients were alive. There was one death on post-cryother-
apy day 1 in a patient who underwent an emergency procedure for complete anastomotic obstruction after left single lung transplantation. Death was due to hypoxia. The patient was moribund at the time of the procedure. The results of cryotherapy were not available in this patient although post-mortem revealed a partially patent airway. The remaining mortalities were late deaths attributable to either bronchiolitis obliterans or infection to immunosuppression.

4. Discussion

Cryotherapy is a well established modality for the palliation of malignant and benign tracheobronchial tumours [20]. It was initially utilised in the pulmonary system to treat intraluminal advanced carcinoma of the trachea or bronchi after other modalities failed [17] having been proven as effective with minimal morbidity and mortality, cryotherapy has become the first-line treatment for obstruction in inoperable pulmonary cancer. Objective improvement in FEV₁ and FVC were shown with subjective improvement in dyspnoea being a common benefit [18, 20]. It was logical to proceed with and assume the efficacy of cryotherapy to treat benign obstructive granulation tissue after lung transplantation for several reasons. Granulation tissue arises histologically from mucosal membranes. The sensitivity of mucosal membranes and the relative resistance of cartilage and connective tissue to cryotherapy is known. Cryotherapy techniques have been developed for intra-bronchial therapy at our institution with low morbidity and excellent patient tolerance.

Past methods of treating this condition have used stent insertion as the primary means of maintaining airway patency. There has been much experience with both rubberised and metallic stents in the literature. Higgins et al inserted 14 stents in 205 patients [13] and Griffith et al stented 12 of 19 stenoses in 164 anastomoses [4]. Brichon et al used 15 metallic endovascular stents in 16 bronchial stenoses with good results. There were 2 patients who had problems with prosthetic area granulomas treated by laser coagulation [8]. Carre stented 4 out of 8 patients after repeated dilation and treated recurrent granulation tissue after stenting with laser therapy and balloon dilation within the Wallstent [9]; 5 of 6 patients in a series from Colt et al required stenting after an attempt at granulation removal by laser coagulation [10]. Within these series there is a high incidence of stent requirement due to failed local control of granulation tissue and problems with prosthetic area granulomas, particularly after silicone stent insertion.

Using cryotherapy as the initial therapy markedly reduced the percentage of patients requiring stents compared to other series. We were unable to predict who would develop long-term strictures based on the onset of granulation tissue or the degree of obstruction. In 8 patients in the series, simple granulation tissue was present with the absence of marked fibrosis. After a treatment regimen of cryotherapy with bronchial dilation, a normal luminal diameter with no long-term recurrences was achieved. The problem of underlying moderate to significant fibrosis was present in 13 patients. In these complex cases, the cryotherapy was successful in removing the obstructive tissue only to uncover a relatively fixed stenosis. Of these patients, 5 were able to be managed by additional dilation. In these patients, the therapy was useful to aid the maturation of the granulation tissue to a healthy scar. In the 6 patients stented after cryotherapy and dilation, resolution of the granulation tissue greatly facilitated endobronchial stent insertion. Initially, patients were treated with temporary bifurcated and Ingutdinuly silicone stents [11]. Permanent Gianturco self-expanding metallic stents were ultimately inserted [14]. In the remaining two cases, cryotherapy was effective in clearing granulation tissue encroaching the lumen through the interstices of the endobronchial metal stent. This treatment regimen has resulted in a 38% stent rate, significantly lower than in other published series.

The measurement used to screen for bronchial obstruction, rejection and bronchiolitis obliterans in our institution are FEV₁ and FVC. Although there is evidence to suggest that bronchiolitis obliterans can be differentiated from bronchial stenosis by flow-volume loop differences [21], we proceed with bronchoscopic evaluation when FEV₁ and FVC are decreased. In this study, cryotherapy achieved near complete restoration of the narrowed lumen rapidly. This was accompanied by significant improvement in pulmonary function tests. This functional improvement was shown in the group which did not require stenting as well as the more difficult airway stenoses which were stented.

Excess formation of granulation tissue in the trachea or bronchi following lung or heart–lung transplantation is not uncommon. It occurs around or below the anastomotic site and is probably a response to ischaemia or infection. Ischaemia is a more common aetiology in double-lung and single-lung transplantation as the blood supply to the distal portion of the anastomosis may be compromised despite omental or internal mammary artery wrapping. Direct revascularisation of the bronchial circulation by internal mammary artery to bronchial artery anastomosis has been a more recent direct attempt to improve tissue healing in this area. One of these three techniques was used in 9 patients in this series (Fig. 1). There was no difference in the time to presentation, duration of required therapy, or the need for subsequent stenting. No direct conclusions can be drawn from this small series concerning prevention of these airway problems without...
direct comparison with a larger transplant group. However, within this series, there was no effect of these procedures in providing resolution to the already existing airway problems. This is supported by results from a prospective randomized trial by Khagani et al showing no difference between omental wrap, internal mammary artery wrap and no wrap groups in a number of airway complications or actuarial survival [5]. Colquhoun et al showed no significant correlation between the type of wrap and airway complications [1]. It remains to be seen as to whether direct revascularisation of the bronchial arteries reduces long-term airway complications.

In conclusions, obstructive airway problems due to granulation tissue after lung transplantation represent a significant clinical challenge often requiring multimodality therapy. This series shows the benefits of using cryotherapy as a first-line approach in these patients. The intraluminal extensions of the granulation tissue were able to be cleared by cryotherapy resulting in improved pulmonary function. The need for adjunctive dilation and ultimate stent placement appears to be related to the degree of fixed obstruction caused by fibrosis and can readily be determined after cryotherapy. This is the first report using cryotherapy in the management of post-lung transplantation airway obstruction. We continue this management in our treatment of these problems.

References


Appendix A. Conference discussion

Dr Haverich (Hanover, Germany): Thank you for these interesting observations. Do you have a comparison to other treatment modalities such as electrocautery or laser techniques?

Mr Zehr: The initial method of removing intraluminal granulation tissue at Harefield was by dissection or electrocautery. We used the laser in several cases but do not have extensive experience with that technique. The advantage of cryotherapy is the relative sensitivity of the granulation tissue to destruction by freezing compared to the relative resistance of cartilage. With the other techniques it is easier to damage the wall of the bronchus or the trachea. Electrocautery also resulted in a higher rate of recurrence and was a messier procedure overall.

Dr Haverich: You told us that once this complication has occurred, the further course of that entity would not be influenced by revascularization procedures being done or not. But what about the incidence, was the incidence less in those where you did revascularize the bronchus?

Mr Zehr: I do not have the data for the total series. However, we have published a randomised prospective study (J Heart Lung Transplant 1994;13:767–73) comparing wrapping the bronchial anastomosis with a mammary artery pedicle, wrapping it with an omental pedicle, and no wrap. There were no differences in anastomotic complications among the three groups. We have more recently directly anastomosed the internal mammary artery to the bronchial artery. The data looks promising in regards to these revascularised patients having improved anastomotic healing and less frequent airway complication and publication is forthcoming.