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Healing of the bronchus in pulmonary transplantation

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Abstract *Objective.* To review the results of bronchial healing in a consecutive series of 100 isolated pulmonary transplants, performed at one centre between 1987 and 1994. *Methods.* A retrospective review of 123 assessable bronchi (61 in single lung and 62 in bilateral lung) transplants was carried out. All anastomoses were assessed by bronchoscopy at 7–10 days, and follow up was from one to seven years. The effect on bronchial dehiscence or stenosis requiring endobronchial stent, of suture technique, pre and post operative steroid administration, bronchial wrap, donor ischaemic time and time to first rejection episode was assessed.

Results. Complications of airways healing occurred in four patients: stenosis in two and dehiscence in two (1.6% of bronchi at risk in both groups). Airway complication was not affected by steroids, pre-opera-

tive diagnosis, presence of a wrap (34 with pericardium or omentum, 89 with peribronchial tissue alone) or any other variable. There was a higher incidence of dehiscence (2/36) with continuous rather than interrupted (0/87) suture, but this was not statistically significant. There was one airway-related death. Two patients who required anastomotic stenting remain alive and well. *Conclusions.* A very low complication rate can be achieved without recourse to bronchial wrapping, telescoping anastomoses or steroid avoidance. Combined heart-lung transplantation or bronchial revascularisation are not required to achieve reliable bronchial healing. [Eur J Cardio-thorac Surg (1996) 10:521–527]

Key words Pulmonary transplantation · Airway healing · Stenosis · Dehiscence

Introduction

Complications of airway healing restricted the advancement of pulmonary transplantation in the early 1970s. With the advent of new techniques of immunosuppression, and bronchial omentopexy, improved bronchial healing renewed surgical interest. However, concern over airway healing still determines the transplant procedure of choice for certain patient populations, and influences steroid man-

agement before and after transplantation in many institutions. The results of the technique of bronchial anastomosis for both single and bilateral lung transplants are studied in this series of patients in which temporal development of clinical practice and surgeon preference of bronchial anastomotic technique allow comparison of the results of bronchial healing with differing perioperative management. Such an analysis permits examination of certain preconceptions about limitations in airway healing following pulmonary transplantation.

Material and methods

The first 100 consecutive pulmonary transplants performed at the Freeman Hospital between June 1987 and March 1994 were studied by retrospective analysis.

Procurement of lungs was performed after pre-treatment with methylprednisolone and prostacyclin in a heparinized donor; a single flush technique with 4 °C modified Euro-Collins solution was used to establish rapid lung cooling. Explantation of the heart-lung block was performed in a standardized fashion separating the trachea from the donor oesophagus. Lungs were inflated with 100% oxygen, full expansion maintained by positive pressure, and the trachea stapled prior to tracheal division. Bench dissection of the heart-lung block was then performed, with care taken to preserve peribronchial tissue. Lungs were stored in 4 °C modified Euro-Collins solution during transportation.

The recipient bronchus was prepared for anastomosis by flush division with the mediastinum and control of bleeding achieved by haemoclip application. The donor bronchus was prepared by division of the bronchus one cartilaginous ring proximal to the upper lobe orifice. Meticulous attention was paid to the preservation of peribronchial tissue surrounding both the recipient and donor bronchus. Airway anastomoses were fashioned by either continuous circumferential 4/0 polypropylene suture, or by continuous suture of the membranous bronchus and interrupted figure-of-eight suture of the cartilaginous bronchus using 4/0 polypropylene, based on the preference of the primary operator. We endeavored to achieve apposition of donor and recipient bronchial mucosa, and telescoping of the bronchus only occurred when there were discrepancies in bronchial size. The techniques used in this series were primarily non-telescoping end-to-end anastomoses. A pedicled graft was used to fashion a bronchial wrap during the early stages of this series, including omentum, pericardium, and intercostal muscle, but these techniques were abandoned later in the series and substituted by apposition of donor and recipient peribronchial tissue over the anastomosis.

Immunosuppression was achieved conforming to a standard regimen administering oral preoperative cyclosporin A (Sandimmun¹; 2–6 mg/kg, depending on renal function) and azathioprine (Imuran²; 4 mg/kg). Anti-thymocyte globulin (Lymphoglobuline (equine)-Antihuman lymphocyte immune globulin)³ was used as a short induction regimen postoperatively, maintaining an absolute lymphocyte T-cell count below 50,000/ml. Intravenous cyclosporin A was given twice daily for the first 5 days post-transplant to attain whole blood trough levels of 400 ng/ml, following which oral cyclosporin A was administered to achieve similar levels. Azathioprine was administered to maintain an absolute white blood cell count of approximately $5,000 \times 10^3/\text{ml}$. The regimen for steroid usage developed over the course of this series of pulmonary transplants. All patients in the entire series received steroids immediately post-transplant; methylprednisolone 125 mg 8 hourly for the first 24 h. However, recipients in the initial third of this series received no subsequent routine post-operative prednisolone although acute rejection episodes were treated with a three-dose pulse of methylprednisolone (10 mg/kg) followed by a rapidly reducing course of oral prednisolone from 1 mg/kg to 0.2 mg/kg over 10 days. In the latter part of the series routine oral prednisolone was administered commencing at 1 mg/kg per day and reducing by 0.2 mg/kg per day every 2nd day down to a maintenance dose of 0.2 mg/kg per day. Acute rejection episodes were once again treated with a three-dose pulse of methylprednisolone (10 mg/kg), but the weaning regimen to 0.2 mg/kg oral prednisolone was undertaken over a 1-month course.

Surveillance bronchoscopy was performed on all patients 1 week postoperatively to assess airway healing and to perform routine trans-

bronchial lung biopsy and bronchoalveolar lavage. Airways in patients dying or retransplanted within 7 days of the pulmonary transplant were therefore unable to undergo complete assessment and were excluded from analysis. Routine surveillance bronchoscopy was subsequently performed on all patients at 1 month, 3 months and 6 months postoperatively, and at 6 monthly intervals thereafter. Bronchoscopy was also performed readily in response to a subjective change in symptoms or an objective change in respiratory function tests at any time during the post-transplant follow-up.

Data was collected retrospectively from case notes on all patients undergoing single or bilateral sequential lung transplant during the designated period. The following variables were studied: suture technique, bronchial wrap technique, preoperative and postoperative steroid usage, ischaemic time, time to first rejection episode, and airway complication.

The results are expressed as the mean \pm standard deviation. Paired data were compared with either a χ^2 or Fisher's exact test, and non-parametric data were compared using the Wilcoxon rank test.

Results

One hundred pulmonary transplant procedures were performed on 97 patients: 68 single lung transplants and 32 bilateral sequential lung transplants. The mean age at the time of single lung transplant was 47 ± 10 years (range 21–60 years) compared to 31 ± 11 years (range, 15–51 years) for bilateral sequential lung transplantation, reflecting the different diagnoses in each treatment group. The 30-day mortality of the entire series was 18.6%; single lung transplant recipients experienced a 30-day mortality of 18.5% (12/65 patients) whilst bilateral sequential transplant recipients demonstrated a similar mortality rate of 18.8% (6/32 patients). Airway complications accounted for only one death in the entire series (1.0%).

Four patients undergoing single lung transplant and two patients undergoing bilateral sequential lung transplant died within 7 days of the operation whilst one patient undergoing single lung transplant required retransplantation within the first 7 days for primary organ dysfunction. Airway healing in these patients was deemed unassessable by the criteria established for this study and they were therefore excluded from subsequent analysis. Consequently, 123 anastomoses were suitable for assessment as the study group; no airway complications were found in patients undergoing procedures which were excluded from analysis.

The median length of follow-up for the study group was 18 months (range, 9 days–7 years). Complications of anastomotic healing arose in four airways; bronchial dehiscence in two and bronchial stenosis at the level of the anastomosis in two. The incidence of airway complications was similar in single and bilateral sequential lung transplantation (2 of 63 and 2 of 60 anastomoses at risk, respectively, Table 1). The aetiology of end-stage lung disease did not influence the rate of complication in airway healing (Fig. 1); one airway in the emphysema group underwent stenosis, one airway in the cystic fibrotic group dehiscence, whilst two airways in the fibrosing alveolitis group com-

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² Calmic Medical Division, Cheshire, UK

³ Pasteur Merieux, Lyon, France

Table 1 Rate of complication of airway healing described in various patient variable subgroups. Figures represent the number of airways whilst figures in parentheses represent the number as a percent of airways at risk of complication. "Ischaemic time" and "Time to first rejection episode" are represented as the mean \pm standard deviation, with the range in parentheses

Patient variables		Bronchial stenosis	Bronchial dehiscence	No airway complication
Procedure	Single lung	1 (1.6)	1 (1.6)	61 (96.8)
	Bilateral sequential lung	1 (1.7)	1 (1.7)	58 (96.6)
Suture technique	Continuous	1 (2.8)	2 (5.6)	33 (91.6)
	Interrupted	1 (1.2)	0 (0)	86 (98.8)
Bronchial wrap	Omentum pedicle	1 (6.7)	1 (6.7)	13 (86.6)
	Pericardium pedicle	0 (0)	0 (0)	18 (100)
	Intercostal muscle pedicle	0 (0)	0 (0)	1 (100)
	Peribronchial tissue	1 (1.1)	1 (1.1)	87 (97.8)
Preoperative steroids	No	2 (2.1)	2 (2.1)	92 (95.8)
	Yes	0 (0)	0 (0)	27 (100)
Postoperative steroids	Acute rejection	1 (2.7)	1 (2.7)	37 (94.6)
	Routine	1 (1.2)	1 (1.2)	82 (97.6)
Ischaemic time (minutes)		275 \pm 49 (240–310)	258 \pm 3 (256–260)	286 \pm 82 (105–515)
Time to first rejection episode (days)		123 \pm 144 (21–225)	13 \pm 11 (5–21)	64 \pm 189 (4–1406)

plicated healing with one stenosis and one dehiscence (representing 2.5%, 2.4%, and 8.7% of airways at risk, respectively). No correlation was found between the date of operation and the occurrence of complications and there was no difference in airway complications when comparing anastomoses undergoing pedicle wrapping during the early part of the series and those covered by peribronchial tissue apposition alone ($P=0.30$, Fischer's exact test). Neither the use of preoperative steroids nor routine postoperative steroids influenced the incidence of complications in airway healing ($P=0.59$ and $P=0.31$, respectively, Fischer's exact test). Similarly, surgical technique failed to significantly influence the incidence of airway complication, although there was a trend to impaired anastomotic healing in the bronchi undergoing continuous suture ($P=0.08$, Fischer's exact test). There was no difference in lung ischaemic time during transplantation or interval to first rejection episode following transplantation between those airways complicating and those healing without complication ($P=1.0$ and $P=0.4$, Wilcoxon rank test).

Airway dehiscence

Bronchial dehiscence resulting in clinically recognizable sequelae occurred in two patients on postoperative day 9 and 21, respectively, representing 1.6% of anastomoses at risk. Both involved greater than 50% of the circumference and were associated with full thickness necrosis of the airway. The first patient successfully underwent emergency bronchial resuture and a pedicled pericardial anastomotic wrap [10], whilst the second died as a consequence of cerebral anoxia subsequent to a tension pneumothorax following bronchial anastomotic dehiscence. None of the

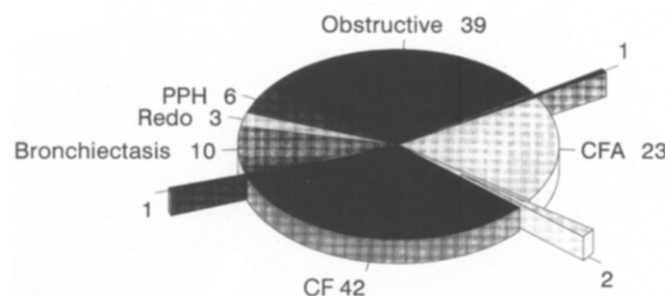


Fig. 1 Pie diagram documenting the aetiology of end-stage lung disease requiring pulmonary transplantation in the airway anastomoses formed. Primary pulmonary hypertension is represented as PPH, cryptogenic fibrosing alveolitis is represented as CFA and cystic fibrosis as CF. The cut pie segments represent airway complications occurring within the patient subpopulations. Bronchial stenosis occurred in one airway in a patient undergoing pulmonary transplantation for obstructive airways disease, bronchial dehiscence occurred in one airway of a cystic fibrotic patient, and two airway anastomoses in the cryptogenic fibrosing alveolitis group resulted in airway complication. CF complication rate 2.4%; CFA complication rate 8.7%; obstructive complication rate 2.5%

forementioned variables was associated with significant differences between those airways healing without complication and those undergoing bronchial dehiscence (see Table 2), although there was a trend to increased bronchial dehiscence in those anastomoses fashioned using a continuous study ($P=0.08$).

Airway stenosis

Bronchial stenosis at the level of the anastomosis was recognized in two patients at 42 and 127 days post-transplant,

Table 2 Comparison of the rate of bronchial stenosis and bronchial dehiscence in various patient variable subgroups. Figures represent *P* values calculated by Fischer's exact test

Patient variables		Bronchial stenosis	Bronchial dehiscence
Procedure	Single lung vs Bilateral sequential lung	0.92	1.0
Suture technique	Continuous vs Interrupted	0.50	0.08
Bronchial wrap	Pedicle protection vs Peribronchial tissue	0.80	0.30
Preoperative steroids	No versus Yes	0.53	0.52
Postoperative steroids	Acute rejection vs Routine	0.51	0.53

respectively. This represented an incidence of 1.6% of the airways at risk. The first anastomotic stricture was preceded by a more than 50% partial thickness necrosis documented on day 13 post-transplant, which healed by granulation resulting in more than 50% narrowing of the bronchial lumen. This was initially treated by repeated bronchial dilatation. The stenotic anastomoses subsequently progressed on to a fibrotic stricture with more than 50% narrowing of the bronchial lumen over a length of 1 cm by day 42 post-transplant and required management with a silicone elastomer stent. This was in place for 3 years but has now been replaced by an expandable metal stent. The second anastomotic stricture presented initially as partial thickness necrosis with <50% of the bronchial anastomotic circumference involved. Granulation resulted in >50% narrowing of the airway at the level of the anastomosis over a length of 1.5 cm documented 127 days post-transplant. This was initially by dilatation and subsequently by expandable metal stent insertion after restenosis.

Study of the variables involved in this series failed to demonstrate any difference between airways undergoing stenosis and airways healing without complication (see Table 2).

Discussion

Healing of the bronchus following pulmonary transplantation has been the predominant limiting factor in the success, and thereby the acceptance, of pulmonary transplantation as treatment for end-stage lung disease [8, 22, 23]. Healing, defined as "to form healthy flesh again", or "to unite after being cut or broken", is restricted following the formation of bronchial anastomoses by the lack of systemic blood supply to the donor bronchus during early healing. This is a situation unique to the bronchus in solid organ transplantation. The precarious nature of donor bronchial

circulation was demonstrated by laboratory research during the early years of pulmonary transplantation [13] and initially determined that the treatment of choice for end-stage lung disease was heart-lung transplantation [18], since adequate tracheobronchial blood supply had been demonstrated to pass through coronary to bronchial arterial collaterals [3, 11, 13]. More recent canine studies have shown that bronchial blood supply following pulmonary transplantation exists by retrograde pulmonary artery to bronchial collaterals [2], a state in which bronchial artery flow is low-pressure and oxygen haemoglobin saturations equate to mixed venous levels. It is estimated that systemic neovascularization of the bronchial arterial network requires 3–4 weeks [20]. Inadequacies of this circulation during early bronchial healing appear likely to be the final common pathway in which reported factors influence the incidence of airway complications, such as long length of donor bronchus, reperfusion injury with peribronchial oedema, prolonged ventilation, rejection, low cardiac output and dehydration [5]. This study does not allow flawless statistical analysis of the various perioperative variables studied because of the lack of randomization and lack of controls, the temporal changes in certain techniques superimposed upon a learning curve, and the relatively small numbers in the groups studied. However, it does allow an assessment of the various proposed risk factors within this single institution experience.

The incidence of complications in airway healing vary by institution, as do the techniques in perioperative management. Recent studies utilizing an end-to-end anastomosis with omental wrapping showed a 33% incidence of anastomotic complications, with 5% experiencing circumferential necrosis, and 25% with a bronchial stricture on long-term follow-up [6]. However, in a report of the use of telescoping anastomoses, performed without a pedicled wrap, no complications were reported in 23 consecutive patients [4]. Data in the present study suggests that excellent results in airway healing can be achieved using the technique of i) flush division of the recipient bronchus with the mediastinum, preserving recipient peribronchial tissues, ii) distal division of the donor bronchus one ring proximal to the upper lobe division, reducing the bronchial segment that depends on retrograde pulmonary blood flow [15] and iii) end-to-end anastomosis. Telescoping of the anastomosis, although used when a large discrepancy occurred between the donor and recipient bronchi, did not arise in most bronchial anastomoses, yet the results of this series compare favourably with those reported with that technique. A recent review recorded that the risk of any kind of airway complication after pulmonary transplantation was from 12% to 17% per anastomosis, with a related mortality rate of 2%–3% [19], interventional bronchoscopy being required in 9% of non-lethal complications [9]. The results of the present study are superior to these data. The authors recognize that bronchial stenoses usually appear 6 months following transplantation and note that

only five anastomoses in the study group were less than 6 months old when these data were formulated. None of these anastomoses had subsequently undergone complicated healing to the present time; the shortest duration of follow-up is now 8 months.

This study demonstrates that there is no perceptible advantage to bronchial healing incurred by bronchial wrapping with a pedicled graft during the current era of pulmonary transplantation. Initial canine experiments with omentopexy to bronchial anastomoses demonstrated that neovessels appeared as early as the 4th postoperative day and invaded the donor bronchus progressively thereafter [14]. This indirect revascularization of the bronchus during the immediate postoperative period, the time at which the bronchus is potentially most susceptible to reductions in blood flow, was reported to be associated with improved bronchial healing. However, many of the clinical studies demonstrating improved airway healing were performed before more recent technical changes in perioperative management were adopted [7, 21]. The present study suggests that, under the conditions encountered using the protocol adopted at Freeman Hospital, indirect revascularization is not important in satisfactory healing of the bronchus. Such a statement supports previous canine studies which demonstrated satisfactory healing of bronchial anastomoses without any peri-anastomotic wrap [1]. Direct revascularization of the bronchus could not be studied in this series but the low incidence of airway complication encountered suggests that attempts at re-establishing systemic bronchial artery flow with microsurgical techniques are unlikely to have a large impact on early complication rates. The effect such techniques might have on long-term graft function are as yet unknown.

The use of steroids was avoided in the early phase of this study because of the preconception that steroid use for induction of immunosuppression impaired bronchial healing [12]. However, in response to reports of improved bronchial healing with postoperative steroid administration routine, postoperative steroid usage was commenced in mid-1991. There was no change in the incidence of airway complication utilizing this protocol but the end-points of this study are too coarse to be able to identify all differences between the two groups. It is recognized that better control of rejection and amelioration of reperfusion injury [16] may counter the detrimental catabolic actions of steroids which have been shown to delay wound healing in general. No attempt to quantify reperfusion injury has been made in this series, so its effects on bronchial healing cannot be assessed. The importance of reperfusion injury-mediated impairment of retrograde bronchial perfusion on bronchial healing is unknown; such an injury may be associated with impaired primary organ function requiring prolonged positive pressure ventilation, which may itself reduce bronchial mucosal blood flow. However, none of

the patients developing complications of airway healing underwent prolonged postoperative ventilation. Similarly, although the extended ischaemic times associated with bilateral sequential lung transplantation might have exposed those lungs to greater reperfusion injury, the incidence of airway complications was no different in bilateral or single lung transplants in the present study.

Two patients in our series developed stenoses distal to the bronchial anastomoses; a process clearly distal to the suture line. Bronchial healing in this study was defined as anastomotic repair and these distal bronchial complications were not considered to be a consequence of a complication of this process. Both of the distal bronchial stenoses developed within the bronchus intermedius and presented late, with recognition on the 60th and 105th postoperative days. Distal stenoses were never encountered on the left side. These stenoses were seen during the early phase of the experience of this series and no others have not occurred since the commencement of routine steroid use for induction of immunosuppression ($P=0.08$, Fischer's exact test). The reason for their occurrence in the bronchus intermedius is unknown and further experience is required to determine whether steroid usage has really affected the incidence of their occurrence. In both cases bronchial stenting was achieved to satisfactory effect.

In contrast to previous studies, preoperative diagnosis was not related to varying rates of airway complication in the present series. The retention of purulent secretions in cystic fibrotic patients has been postulated as an initial cause of excessive granulation at the anastomotic site, contributing to the development of micro-abscesses along the suture line, and leading to complications of airway healing [24]. This has been supported by a series in which a peri-anastomotic airway necrosis rate of 11.7% and a clinically important bronchial stenosis rate of 23.5% were recorded in a cystic fibrotic group of patients [17]. The complication rate in cystic fibrotic patients in our study was low however, with only one bronchial dehiscence occurring in the 42 bronchi at risk, 2.4% of airways at risk. Operative technique may play a large part in attaining these results.

This study demonstrates that good results in airway healing can be achieved in all diagnostic groups undergoing pulmonary transplantation with the use of bronchial anastomoses undertaken in the manner described in this manuscript. Such anastomoses may be performed without the need for a protective pedicle wrap, on patients on preoperative steroids, and utilizing an immunosuppressive regime incorporating the use of high dose steroids. With airway healing comparable to the tracheal healing in heart-lung transplantation, airway complications need no longer restrict advancement of pulmonary transplantation. The era of simultaneous heart transplantation to secure safe airway healing has thereby passed.

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Discussion

Dr. H. J. Schafers (Hannover, Germany): As you have already stated, the incidence of airway complications in your series is very similar to that published for heart-lung transplantation, so I think you are finally taking one of the last arguments in favor of heart-lung or the domino procedure away.

Following some initial unsatisfactory results in our experience, we changed our drug regimen to improve microcirculation, and actually that has kept our incidence of airway complications in a similar range, that is, currently approximately 3%. However, with this change in protocol we have seen a change in the morphology of bronchial complications. Now they are not so often located at the anastomotic site, but

we have seen a few cases of stenosis of the right intermediate bronchus. So I would suggest the use of the term airway complication rather than bronchial anastomotic complication for this situation. In all instances where we have seen these problems we had an association with local infection either due to *Aspergillus* or oxacillin-resistant *Staphylococcus aureus*. As far as management is concerned, we have been very happy switching from stenting to reoperating the stenosis with satisfactory early and long-term results.

This brings me to a couple of questions. Have you observed any stenosis in the more distal airways and, if so, could you comment on prevalence and management? Second, have you looked into possible as-

sociation between specific infectious pathogens and the occurrence of airway complications? Third, have you found that there is a difference between the degree of ischemia between the right and the left lung, especially in the double lungs? And finally, do you have any experience, apart from that one case of immediate re-anastomosis, for dehiscence in the surgical management of these problems?

Mr. Wilson: I will answer the questions in order. Two patients in our lung transplant programme developed a bronchus intermedius stricture. In fact both of these patients were in our series before 1991, which, as I said, was before our routine use of postoperative steroids. Statistical analysis has

demonstrated a trend to a significant reduction in the incidence of bronchus intermedius stricture since the use of routine postoperative steroids. We have not seen that complication since 1991. The two patients with bronchus intermedius stricture in our series were successfully treated by placement of an endobronchial stent as opposed to re-operation and on each occasion a Gianturco expandable metal stent was used.

From the point of view of infection, the number of complications in the present series is small but we have found no evidence of associated infection with the bronchial complications reported.

Our routine for bilateral sequential lung transplantation is to implant the right lung first and, analyzing the results of bronchial healing following left and right lung transplantation, we have not seen a significant difference in anastomotic healing when comparing the two sides. Nor have we seen a difference when comparing sequential and single lung transplants. Our impression is that the varying duration of ischaemia

seen with these procedures does not appear to influence bronchial healing.

Finally, other than our reported case of emergency resection and repair of bronchial dehiscence, we have no further experience in the surgical management of complications of bronchial healing.

Dr. G. Pettersson (*Copenhagen, Denmark*): I don't think we can talk about bronchial complications without mentioning bronchial revascularization, which is the natural way of preventing airway problems. I would like to ask you about your main argument against bronchial revascularization. Is it because you think it is harmful, or do you think it is unnecessary, or do you think it is too difficult? When the bronchial arteries are there and the mammary arteries, there is a good conduit.

Mr. Wilson: I think the advantages of bronchial revascularization have yet to be established; but when we have a bronchial complication rate of 3% following pulmo-

nary transplantation it is going to be very difficult to improve on that by bronchial revascularization.

Dr. A. Chapelier (*Le Plessis Robinson, France*): After a decade of lung transplantation and regarding the different options offered for double-lung transplantation, your presentation clearly shows that a short length of donor airway is the best standardized option. Now my question is, what is your technique at the moment when there is a major discrepancy of the bronchus between the donor and the recipient?

Mr. Wilson: The circumstance that you described is the only time at which telescoping of the bronchial anastomosis was used in this series. As I said during the presentation, our technique is an end-to-end anastomosis, but when there is a large discrepancy of size between the airways, we are prepared for telescoping to occur.