Original articles

European Journal of Cardiothoracic Surgery
© Springer-Verlag 1991

Eur J Cardio-thorac Surg (1991) 5:561–565

Bronchial circulation after experimental lung transplantation: the effect of direct revascularization of a bronchial artery *

M. Aoki [1], H.-J. Schäfers [2], K. Inui [1], N. Klipsch [2], S. Demertzis [2], J. Kotzerke [3], A. Haverich [2], and H. Wada [1]

[1] Kyoto Chest Disease Research Institute, Kyoto University, Kyoto, Japan
[2] Division of Thoracic and Cardiovascular Surgery, Surgical Center, Hannover, FRG
[3] Department of Nuclear Medicine, Hannover Medical School, Hannover, FRG

Abstract. Direct revascularization of a bronchial artery has been proposed as a measure to alleviate the problem of bronchial ischemia after lung transplantation. To assess the effect of restoration of arterial blood flow to the transplanted bronchus, bronchial mucosal blood flow was measured in a model of modified unilateral lung transplantation in pigs. Laser Doppler velocimetry (LDV) and radioisotope studies using radio-labeled erythrocytes (RI) were used to measure blood flow at the donor main carina (DC) and upper lobe carina (DUC) after 3 h of reperfusion. The recipient carina was used as a reference point; values obtained by LDV and RI were expressed as percentage of blood flow at the recipient carina. Two groups of animals were studied. In group 1 ($n=6$) standard unilateral transplantation was performed; in group 2 ($n=6$) a left bronchial artery was reimplanted into the descending thoracic aorta of the recipient. No differences were observed between the two groups with respect to preoperative or postoperative gas exchange or hemodynamics. In group 1, bronchial blood flow at the DC was 37.6±2.2% (LDV) and 44.1±14.8% (RI) of reference blood flow. At the DUC, blood flow was 54.9±7.7% (LDV) and 61.6±25.7% (RI) of normal flow. In group 2, blood flow was increased at the DC as measured by LDV (55.3±17.1%; $p<0.05$) and by RI (60.8±25.3%; $p<0.2$). A similar increase was found at the DUC (LDV: 81.8±19.3%; $p<0.05$; RI: 88.6±31.0%; $p<0.2$). It is concluded that there is a significant gradient of blood flow from intra- to extrapulmonary airways after lung transplantation. Reimplantation of a bronchial artery results in significant improvement of graft bronchial blood flow. Restoration of bronchial perfusion to normal levels, however, cannot be achieved, suggesting a possible defect in the microcirculation of the donor airways. [Eur J Cardio-thorac Surg (1991) 5:561–565]

Key words: Lung transplantation – Bronchial blood flow – Bronchial artery revascularization

Both unilateral and bilateral pulmonary transplantation have become a realistic option for many patients with terminal pulmonary disease and preserved cardiac function [2, 4, 16]. One of the major sources of early morbidity and mortality, however, is the occurrence of airway complications [12, 15]. A number of experimental investigations have identified ischemia of the donor bronchus as the most important reason for the occurrence of bronchial complications [6, 9, 10, 14]. Deprived of its physiologic arterial blood supply, the transplanted airway depends on retrograde perfusion from bronchopulmonary collaterals in the initial postoperative period. An omental wrap around the graft airway has been proposed and is expected to provide secondary collateral connections to the bronchial vessels within 1 week [10]. Following its clinical use, however, bronchial omentopexy has not been able uniformly to prevent ischemia of the grafted airways. Direct revascularization of a bronchial artery has been proposed to prevent ischemia of the transplanted bronchus [7, 9, 11, 14]. In some experimental investigations improved healing of the bronchial anastomosis has been observed [9, 14].

So far, little information exists on quantitative measurements of blood flow in the extrapulmonary airways following lung transplantation. The present investigation was undertaken to measure bronchial blood flow in pulmonary allografts, focusing particularly on differences between extra- and intrapulmonary airways. In addition, the effect of direct reimplantation of a bronchial artery on bronchial perfusion was studied.

* Supported by the Deutsche Forschungsgemeinschaft

Received for publication: June 20, 1991
Accepted for publication: July 29, 1991

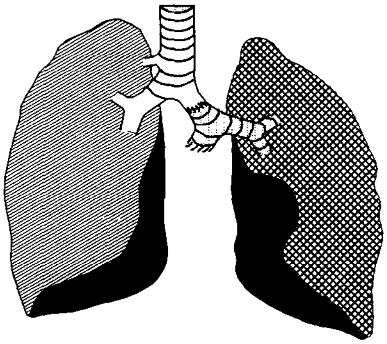

Fig. 1. Schematic drawing of modified left lung transplantation used as experimental model. The distal trachea with main carina and the stump of the right main bronchus are left attached to the left main bronchus of the graft (*shaded*). The airway anastomosis is created between the recipient left main bronchus and the distal donor trachea

Material and methods

Model

The technique of unilateral lung transplantation was modified, leaving the entire left main bronchus, main carina with origin of the right main bronchus, and distal donor trachea in continuity. The airway anastomosis was performed betwen the left main bronchus of the recipient and the donor trachea (Fig. 1). The left upper lobe carina and main carina of the graft were used to measure bronchial blood flow.

Animals and anesthesia

Male pigs with a body weight of 17–25 kg were used as donor and recipient animals. Both donor and recipient animals were premedicated with azaperone (10 mg/kg i.m.), atropine sulfate (0.5 mg i.m.), and metomidate hydrochloride (10 mg/kg i.v.) before endotracheal intubation. They were then placed on a respirator [1] at a tidal volume of 20 ml/kg, a respiratory rate of 15/min, and a positive end-expiratory pressure of 3 cm H_2O. Anesthesia was maintained with 50% oxygen, 50% N_2O, and intravenous injections of fentanyl, metomidate-hydrochloride, and pancuronium. The respiratory rate was adjusted to achieve an arterial PCO_2 of 35–40 mm Hg.

Operative technique

The chest of the donor pig was opened by median sternotomy and the heart-lung block prepared for explantation. A perfusion catheter was placed in the pulmonary trunk following systemic heparinization (300 U/kg). After inflow occlusion and cross-clamping of the ascending aorta, the tip of the left atrial appendage was amputated and the pulmonary arterial bed perfused with modified Euro-Collins solution. During perfusion, a pulmonary arterial pressure of 10–15 mm Hg was maintained. After completed perfusion, the heart-lung block was excised. Ex situ, the heart and the right lung were removed. The stump of the right main bronchus was closed with a running suture (Prolene 4-0) [2], and the left pulmonary artery and a cuff of left atrial wall surrounding the left pulmonary veins were left on the graft for subsequent anastomosis. The lung was then placed in cold Euro-Collins solution until implantation.

When reimplantation of a left bronchial artery was intended, the descending thoracic aorta and the aortic arch were excised en bloc with the heart-lung specimen. Ex situ, the descending aorta was opened on its left lateral wall and the origin of the left bronchial artery identified with a probe (Fig. 2). A button of aortic wall surrounding the origin of this artery was then dissected and the remainder of the aorta removed (Fig. 3).

Fig. 2. Operative photograph of identification of a left bronchial artery. The descending thoracic aorta is incised on its left lateral wall, the orifices of bronchial and intercostal arteries are visualized. A Fogarty catheter is used as a probe to confirm the course of the bronchial artery to the left lung

Fig. 3. Operative photograph of left lung prepared for implantation. A button of aortic wall surrounding the orifice of the left bronchial artery has been isolated for subsequent implantation

In the recipient animal, left thoracotomy was performed through the bed of the resected fifth rib. The lung was mobilized and the pericardium opened anterior to the pulmonary veins. The pulmonary artery and main bronchus were clamped centrally and divided close to the upper lobe take-offs of arterial branches and bronchus, respectively. The left atrium adjacent to the pulmonary venous orifices was partially excluded with a side-biting clamp. The veins were divided and the orifices connected by an incision, creating a common left atrial orifice.

Implantation of the graft began with anastomosis of donor and recipient left atrium using an everting mattress suture (Prolene 5-0) [2]. An end-to-end anastomosis was created between donor and recipient pulmonary artery (Prolene 5-0) [2]. The donor trachea was then shortened to three rings superior to the main carina and an end-to-end anastomosis performed between recipient left main bronchus and graft trachea with a running suture (Prolene 3-0) [2]. Ventilation was started, the pulmonary vascular bed deaired, and the clamps removed.

In cases in which reimplantation of the left bronchial artery was performed, a partial occluding clamp was placed on the proximal descending aorta. A longitudinal incision of about 10 mm was made in the aorta and the button of aortic wall surrounding the donor left bronchial artery implanted.

After complete implantation of the graft, a catheter was placed in the left atrium and a thermodilution catheter inserted into the

[1] Bennett Respiration Unit MA-1B
[2] Ethicon, Hamburg, FRG

pulmonary artery for subsequent determinations of pressures and cardiac output.

Measurement of bronchial blood flow

Pilot experiments had documented hemodynamic stability with stable values for bronchial blood flow over a 3-h period (unpublished data). Subsequent measurements were therefore taken 3 h after reperfusion, when a steady state was assumed. Laser Doppler velocimetry was used for measurement of bronchial mucosal blood flow (Periflux 2)[3]. The details of the procedure and the theoretical principles have been described previously [18]. Blood flow was measured at the main carina and upper lobe carina of the graft; the recipient main carina was chosen as the reference point. At each location, the measurements were repeated 5 times and the mean of these values calculated. Blood flow was then expresssed as flow relative to the reference point (DC/RC, DUC/RC).

Immediately after completion of the LDV measurements, the erythrocytes were labeled in vivo using 370 MBq ^{99m}Tc (activation with Technescan PYP)[4]. Fifteen minutes following the injection of Tc, the animal was killed and the central airways of graft and recipient removed. Segments of the recipient carina, donor carina and donor upper lobe carina were excised corresponding to the measuring points for LDV. Radioactivity of the tissue samples was determined in a scintillation chamber and expressed ad CPM/g tissue. Relative values were calculated for donor carina and donor upper lobe carina, using the recipient carina as reference.

Statistical methods

Mean values ± standard deviations were calculated. Statistical comparison between the two groups was performed using ANOVA[5]. A p-value of less than 0.05 was considered significant.

Results

Six experiments were analysed in group 1 (standard technique) and group 2 (reimplanted bronchial artery). There were no differences between the two groups with respect to preoperative variables (Table 1) or postoperative hemodynamics and gas exchange (Table 2).

In group 1, bronchial blood flow was markedly reduced compared to the reference point (Fig. 4). Using laser Doppler velocimetry, 37.6±2.2% of normal flow was measured at the graft main carina. At the graft upper lobe carina, blood flow was 54.9±7.7% of normal; this value was significantly higher than that obtained at the main carina ($p<0.001$). In radioisotope studies, flow was 44.1±14.8% at the graft main carina and 61.6±25.7% of normal at the donor upper lobe carina.

In group 2, a significantly higher flow was measured at the graft main carina using laser Doppler velocimetry (55.3±17.1%; $p<0.05$). Likewise, perfusion at the upper lobe carina was significantly higher than in group 1 (81.8±19.3%; $p<0.05$). Similar values were obtained by radioisotope studies: at the graft main carina, a flow of 60.8±25.3% of normal was measured; at the upper lobe carina blood flow was 88.6±31.0% of normal. Due to considerable interindividual variation, the differences in flow as measured by labeled erythrocytes were not statistically significant ($p<0.2$).

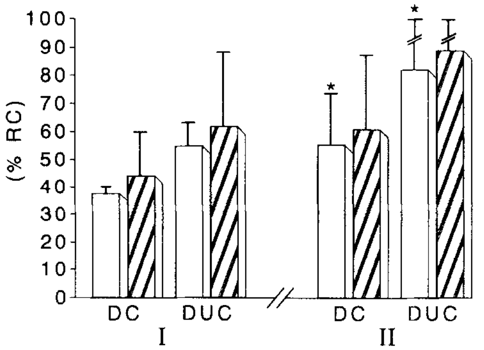

Fig. 4. Relative bronchial blood flow at graft main carina (DC) and graft upper lobe carina (DUC) (percentage of blood flow at recipient main carina). Both laser Doppler velocimetry (*open bars*) and radioisotope studies (*shaded bars*) demonstrate subnormal blood flow in group 1; in group 2, blood flow is significantly enhanced. (* $p<0.05$)

Table 1. Preoperative data for groups 1 and 2

		Group 1	Group 2	p
Donor	weight (kg)	23.3± 3.6	19.8± 0.9	n.s.
	PaO_2 (mmHg)	318 ±28	326 ±35	n.s.
Recipient	weight (kg)	24.5± 1.8	23.3± 1.8	n.s.
	PaO_2 (mmHg)	297 ±36	300 ±25	n.s.
Graft ischemia (min)		131 ±20	123 ±11	n.s.

Table 2. Hemodynamic data and oxygenation 3 h after reperfusion

	Group 1	Group 2	p
Arterial blood pressure (mmHg)	60.2 ± 9.2	56.7 ± 8.0	n.s.
Pulmonary arterial pressure (mmHg)	22.7 ±11.0	19.8 ± 7.3	n.s.
Left atrial pressure (mmHg)	4.0 ± 0.8	3.6 ± 1.6	n.s.
Cardial output (l/min)	2.64± 0.57	1.98±0.46	n.s.
Arterial PO_2 (mmHg)	168.8 ±84.7	149 ±46.2	n.s.

Discussion

Airway complications were one of the main causes of death in early experiences with lung transplantation [8, 9, 17]. A number of experimental and clinical observations indicated that bronchial ischemia was the chief factor responsible for the occurrence of bronchial complications [6, 7, 9, 10, 14]; following lung transplantation, the grafted bronchus is deprived of its physiologic blood supply, depending on retrograde blood flow from bronchopulmonary collaterals for a period of 3–4 weeks [13].

A number of experimental attempts have been made to improve bronchial blood flow. Revascularization of a bronchial artery has been performed both experimentally

[3] Perimed, Stockholm, Sweden
[4] Malinckrodt, Patten, Holland
[5] CSS, STAT SOFT, 2325 East 13th Street, Tulsa, OK 74104, USA

and clinically [7, 9, 11, 14], resulting in improved healing of bronchial anastomoses [9, 14]. Alternatively, a pedicled flap of greater omentum [10] or intercostal muscles [6] has been wrapped around the bronchial anastomosis to provide secondary ingrowth of collateral vessels.

Bronchial omentopexy was introduced into clinical lung transplantation [3]. It was felt that the success with both unilateral and bilateral pulmonary transplantation could be attributed to the use of omentum [2–4]. With increasing experience, however, it became apparent that airway complications still occurred in a significant proportion of patients [12, 15]. They were rarely fatal, but stenosis of the transplanted bronchus occurred, requiring palliative procedures such as placement of endobronchial silicone stents [12, 15]. In all cases, bronchoscopy documented significant ischemia of the transplanted bronchus, suggesting that the formation of collaterals between omentum and bronchial vessels was not sufficient in some cases or developed too late in others. Therefore, alternatives to bronchial omentopexy are required to improve blood flow to the grafted airways.

Even though ischemia of the transplanted central airways has been generally assumed by a number of investigators [9], little data exists on quantitative measurements of retrograde bronchopulmonary collateral flow. One investigation attempted to measure collateral flow in the central airways in situ with isolated perfusion of the pulmonary vascular bed [19]. Using laser Doppler velocimetry, the authors found a perfusion of approximately 50% of normal values at the level of the main carina. This study used nonpulsatile flow, however, which does not fully imitate physiologic blood flow in the pulmonary artery. In addition, this model disregards the surgical trauma of transplantation. Other investigators have measured blood flow at the upper lobe carina of the graft [1, 18] and found a slight reduction of blood flow compared to normal values. The effect of direct revascularization of a bronchial artery on blood flow has not been investigated so far.

The present model was chosen to imitate the clinical situation, with the graft undergoing the typical surgical trauma of transplantation and the pulmonary vascular bed being perfused by pulsatile blood flow. We extended the length of airway transplanted in order to provide information on flow in central parts of the left main bronchus; since in clinical transplantation the airway anastomosis is performed at the level of the main bronchus, this information was considered to be of clinical relevance.

Laser Doppler velocimetry was employed as one method for measuring bronchial mucosal blood flow; its value in the assessment of blood flow of bronchial mucosa has been documented [1, 18]. A drawback of this system is its inability to measure absolute blood flow; in addition, changes in the pressure with which the endoscopic fiber is held on the surface may alter the results. Attempts were made to minimize these drawbacks. The use of a reference point (recipient main carina) allowed determination of relative values without the need for correcting factors between individual experiments. In order to minimize the effect of airway movements on the results, we obtained a stable signal for at least 10 s, and measurements were repeated 5 times, the mean value being accepted for analysis.

The use of radioactive microspheres is an accepted method of assessing relative bronchial blood flow [5]. In the control group in this investigation, however, the blood flow to be measured was to pass the pulmonary vascular bed and bronchopulmonary collaterals before entering the bronchial vascular bed. Therefore, it was uncertain whether microspheres at defined diameters would be able to pass the collateral vessels rather than embolizing in the pulmonary capillaries. Thus, labeled erythrocytes were chosen as "microspheres", representing the most reliable indicator of true bronchopulmonary collateral blood flow to the transplanted airway.

The results obtained in the control group support the assumption that ischemia of the transplanted bronchus is more pronounced in its central portions. Compared to the reference point, parts of the main bronchus only receive approximately 30–40% of their normal perfusion; in addition, this collateral perfusion may be inadequately oxygenated. As a result, tissue oxygen in the central airways may fall below the critical levels required for survival of tissue and adequate healing. To fully investigate oxygen supply to the central portions of the bronchus, tissue PO_2 measurement should be performed, but for technical reasons we considered this to be too difficult in our present investigation. The difference in blood flow between the upper lobe carina and the graft main carina clearly indicates that flow measurements at the upper lobe carina are a poor indicator of perfusion of the central airways.

Reimplantation of the bronchial artery – and thus restoration of bronchial arterial blood supply – resulted in significant improvement of bronchial perfusion both in the central and in peripheral airways. While this was expected, surprisingly, bronchial blood flow only reached approximately two-thirds of normal levels at the graft main carina. Since the patency of the bronchial artery was confirmed by angiography in each experiment, the decrease in flow compared to normal bronchial mucosa can only be explained by the effects of surgical trauma. In particular, a defect in microcirculation within the bronchial arterial bed must be assumed. This may be a consequence of endothelial damage through the high potassium concentrations of the Euro-Collins solution, ischemia, or reperfusion injury. Finally, inadequate preservation of the bronchial vessel at the time of harvesting may be a possibility. Further research will be required in order to identify the factors responsible for the disturbed bronchial microcirculation of pulmonary allograft.

References

1. Aoki M, Wada H, Inui K, Yamazaki H, Hitomi S (1986) Measurement bronchial mucosal blood flow by laser doppler velocimery in the dogs. J Jpn Soc Bronch 8: 622–629
2. Cooper JD, Ginsberg RJ, Goldberg M, The Toronto Lung Transplant Group (1986) Unilateral transplantation for pulmonary fibrosis. N Engl J Med 314: 1140–1145

3. Cooper JD, Pearson FG, Patterson GA, Todd TR, Scully H, Goldberg M (1987) Technique of successful lung transplantation in humans. J Thorac Cardiovasc Surg 93: 173–181
4. Cooper JD, Patterson GA, Grossman R, Maurer J, and the Toronto Lung Transplant Group (1989) Double-lung transplantation for advanced chronic obstructive lung disease. Am Rev Respir Dis 139: 303–307
5. Deffebach ME, Charan NB, Lakshminarayan S, Butler J (1987) The bronchial circulation. Am Rev Respir Dis 135: 463–481
6. Fell SC, Mollenkopf FP, Montefusco CM, Mitsudo S, Kamholz SL, Goldsmith J, Veith FJ (1985) Revascularization of ischemic bronchial anastomoses by an intercostal pedicle flap. J Thorac Cardiovasc Surg 90: 172–178
7. Haglin JJ, Ruiz E, Baker RC, Anderson WR (1973) Histologic studies of human lung allotransplantation. Karger, Basel, pp 13–22
8. Nelems JM, Rebuck AS, Cooper JD, Goldberg M, Halloran PF, Vellend H (1980) Human lung transplantation. Chest 78: 569–573
9. Mills NL, Boyd AD, Gheranpong C (1970) The significance of bronchial circulation in lung transplantation. J Thorac Cardiovasc Surg 60: 866–878
10. Lima O, Goldberg M, Peters WJ, Ayabe H, Townsend E, Cooper JD (1982) Bronchial omentopexy in canine lung transplantation. J Thorac Cardiovasc Surg 83: 418–421
11. Nazari S, Prati U, Berti A, Hoffmann JW, Moncalvo R, Zonta A (1990) Successful bronchial revascularization in experimental single lung transplantation. Eur J Cardio-thorac Surg 4: 561–567
12. Patterson GA, Todd TR, Cooper JD (1990) Airway complications following double lung transplantation. J Thorac Cardiovasc Surg 99: 14–21
13. Pearson FG, Goldberg M, Stone RM, Colapinto RF (1970) Bronchial arterial circulation restored after reimplantation of canine lung. Can J Surg 13: 243–250
14. Pinsker KL, Veith FJ, Kamholz SL, Montefusco C, Emeson E, Hagstrom JWC (1984) Influence of bronchial circulation and corticosteroid therapy on bronchial anastomotic healing. J Thorac Cardiovasc Surg 87: 439–444
15. Schäfers HJ, Haydock DA, Cooper JD (1991) The prevalence and management of bronchial complications following single lung transplantation. J Thorac Cardiovasc Surg 101: 1044–1052
16. The Toronto Lung Transplant Group (1988) Experience with single-lung transplantation for pulmonary fibrosis. JAMA 259: 2258–2262
17. Veith FJ (1978) Lung transplantation. Surg Clin North Am 58: 357–364
18. Yokomise H, Wada H, Inui K, Yamazaki F, Lee M, Aoki M, Hitomi S (1989) Application of laser doppler velocimetry to lung transplantation. Transplantation 48: 550–554
19. Yokomise H, Cardoso PFG, Kato H, Keshavjee SH, Wada H, Slutsky AS, Patterson GA (1991) The effect of pulmonary arterial flow and positive end-expiratory pressure on retrograde bronchial mucosal blood flow. J Thorac Cardiovasc Surg 101: 202–208

Dr. H.-J. Schäfers
Klinik für Thorax-, Herz- und Gefässchirurgie
Medizinische Hochschule Hannover
Konstanty-Gutschow-Strasse 8
W-3000 Hannover 61
Federal Republic of Germany