Bronchial Artery Perfusion Scintigraphy to Assess Bronchial Artery Blood Flow After Lung Transplantation

Martin A. Nørgaard, Niels Gadsbøll, Fritz Efsen, Birger Hesse, Alan Rabøl and Gösta Pettersson

Departments of Thoracic and Cardiovascular Surgery, Cardiology, Radiology, Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital, (Rigshospitalet), Denmark

The bronchial arterial system is inevitably interrupted in transplanted lungs when removing the organs from the donor, but it can be reestablished by direct bronchial artery revascularization (BAR) during implantation. The purpose of this study was to visualize and quantify the distribution of bronchial artery perfusion after en bloc double lung transplantation with BAR, by injecting radiolabeled macroaggregated albumin directly into the bronchial artery system. **Methods:** BAR was performed using the internal mammary artery as conduit. Patients were imaged 1 mo (n = 13) or 2 y (n = 9) after en bloc double lung transplantation with BAR. Immediately after bronchial arteriography, 100 MBq macroaggregated albumin (45,000 particles) were injected through the arteriographic catheter. Gamma camera studies were then acquired in the anterior position. At the end of imaging, with the patient remaining in exactly the same position, ^{81m}Kr-ventilation scintigraphy or conventional intravenous pulmonary perfusion scintigraphy or both were performed. Images were evaluated by visual analysis, and a semiquantitative assessment of the bronchial arterial supply to the peripheral parts of the lungs was obtained with conventional pulmonary scintigraphy. **Results:** The bronchial artery scintigraphic images showed that the major part of the bronchial arterial flow supplied central thoracic structures, but bronchial artery perfusion could also be demonstrated in the peripheral parts of the lungs when compared with conventional pulmonary scintigraphy. There were no differences between scintigrams obtained from patients studied 1 mo and 2 y post-transplantation. **Conclusion:** Total distribution of bronchial artery supply to the human lung has been visualized in lung transplant patients. This study demonstrates that this nutritive flow reaches even the most peripheral parts of the lungs and is present 1 mo as well as 2 y after lung transplantation. The results suggest that bronchial artery revascularization may be of significance for the long-term status of the lung transplant.

Key Words: blood flow; scintigraphy; bronchial artery revascularization

J Nucl Med 1999; 40:290–295

In spite of theoretical advantages and the availability of a reliable surgical method (*1*), the role of direct bronchial artery revascularization (BAR) in lung transplantation is still debated and questioned. Lung transplantation with BAR was originally introduced in Bordeaux (*2*) and London (*3*), and from the beginning has been the standard method for lung transplantation at our institution (*1,4,5*). The primary objective of BAR was to improve blood supply to the airways and thereby facilitate healing. Restoring bronchial artery blood flow in the transplanted lungs, however, may have clinical implications beyond preventing airway ischemia and necrosis.

We have previously reported on the surgical and arteriographic anatomy of the bronchial arteries as observed during surgery and as demonstrated by mammary-bronchial arteriography after lung transplantation with BAR (*6,7*) (Fig. 1). Arteriography visualizes bronchial arteries no smaller than 400–500 μm in diameter, providing limited information about flow distribution and distal supply areas. The most peripheral bronchial arteries, with diameters ranging from 400 down to 10 μm, have been uncharted areas.

This study reports results obtained by bronchial artery perfusion scintigraphy, which has not previously been applied to the bronchial artery circulation.

MATERIALS AND METHODS

Patients

Twenty-two patients who had received en bloc double lung transplants with BAR were scheduled for routine arteriography (9 women, 13 men; mean age, 50 y; range, 28–63 y). Thirteen patients were studied 1 mo post-transplantation, and 9 patients were studied 2 y post-transplantation. We have previously published our clinical results from en bloc double lung transplantation with BAR (*1,5*).

Ethics

The protocol was made according to the Helsinki II declaration and approved by the local ethical committee. The radiation dose was 2.4 mSv per patient.

Surgical Method for Lung Transplantation with BAR

Organ procurement was performed en bloc with the esophagus and descending aorta. Revascularization was performed by anastomosing the distal end of the internal mammary artery to as many bronchial artery orifices as possible in the descending aorta. Even though the ultimate goal was revascularization of all bronchial arteries, revascularization of one large artery was considered acceptable.

Received May 4, 1998; revision accepted Jul. 16, 1998.

For correspondence or reprints contact: Martin A. Nørgaard, MD, Department of Cardio-Thoracic Surgery, RT 2152, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.

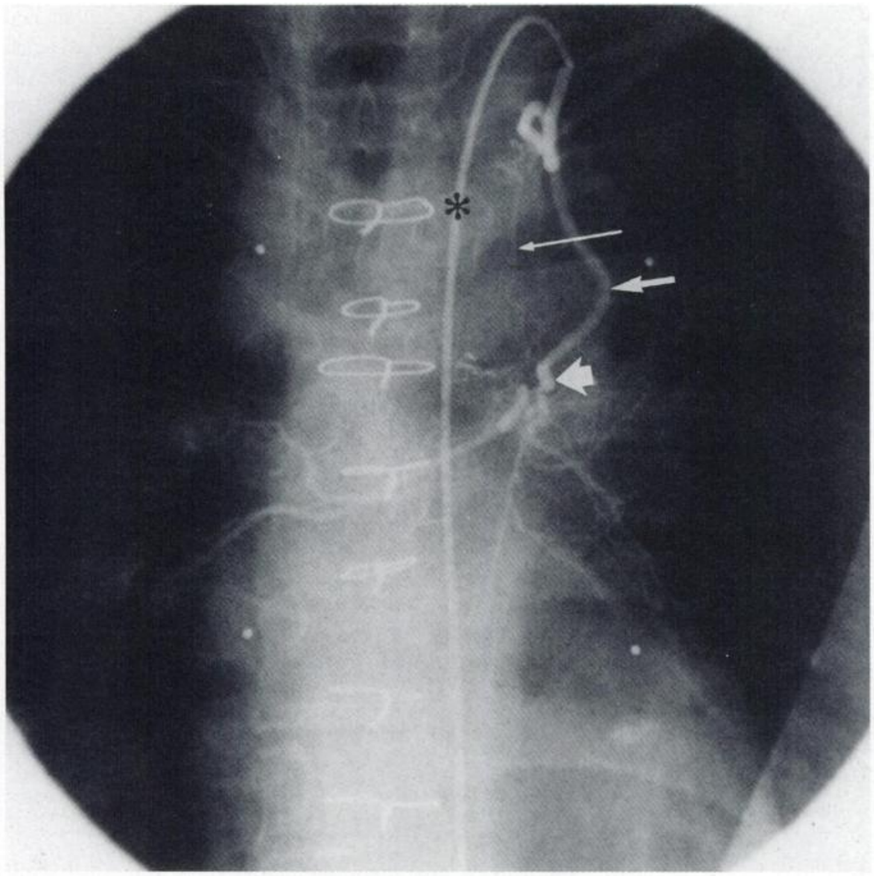

FIGURE 1. Mammary-bronchial arteriography. Asterisk: arteriography catheter (6F). Thin arrow: pericardial vessel leaving mammary artery proximal to mammary-bronchial artery anastomosis. Intermediate arrow: left internal mammary artery (conduit). Thick arrow: left internal mammary–bronchial artery anastomoses.

Arteriography

To evaluate the immediate success and patency of the internal mammary artery conduit and the BAR, mammary-bronchial arteriographies were routinely performed approximately 1 mo and 2 y after the transplantation.

After puncture of the right femoral artery by the Seldinger technique, the tip of a 6F Cordis internal mammary catheter (Cat. no. 532 623; Cordis, Europe, Roden, Holland) was advanced, under fluoroscopic control, to the origin of the left internal mammary artery used as conduit. Care was taken that the catheter did not occlude the lumen of the mammary artery, allowing continuous arterial perfusion along the catheter. Using hand injection of 6–8 mL of contrast medium (Ultravist 370 mg I/mL; Schering, Berlin, Germany), cinematographic recordings were performed in the antero-posterior (Fig. 1), lateral, 45° left anterior oblique and 45° right anterior oblique projections. The arteriographic result (BAR success) was classified according to our previously published classification system (*6*). In brief, this classification grades the degree of surgical success and completeness of the bronchial artery supply to all parts of the lungs:

Complete BAR means that each lung lobe was supplied by at least one lobar branch artery.

Incomplete BAR means visualization of bronchial arteries to the transplanted lung(s), but with one or more lobar branch arteries missing.

Poor BAR (a subgroup of incomplete BAR) means sparse visualization of a few small central bronchial arteries but no lobar branch arteries.

Scintigraphy

Immediately after the arteriography, while the tip of the catheter was still located in the internal mammary artery, approximately 45,000 macroaggregated human albumin particles (Technescan Lyo macroaggregated albumin, Petten, Holland), 95% measuring 10–100 μm, radioactively labeled with 100 MBq ^{99m}Tc and suspended in 5 mL isotonic saline, were injected slowly (3–5 min) through the catheter. Care was taken to avoid retrograde flow of the tracer from the mammary artery into the subclavian artery. This tracer was used in patients 1–20.

To study a possible influence of the variation in particle size of the macroaggregated albumin, a different tracer with a more homogeneous particle size (10–50 μm HAM; TCK-5 CIS; Bio International, Gif-Sur-Yvette, France) was used in the last two patients (21 and 22). Approximately 50,000 particles suspended in 0.3 mL isotonic saline labeled with 100 MBq ^{99m}Tc were injected as described above. After injection the catheter was removed.

Gamma camera imaging was performed in the anterior view with the patients in the supine position (General Electric 400 AC with a parallel-hole, low-energy, general-purpose collimator, Milwaukee, WI). In the first 6 patients, we also aquired gamma camera images in the posterior and two posterior oblique views. Acquisition time was 4 min in each of these projections. However, because the posterior and oblique views were not found to add important information, we obtained only anterior views in the last 16 patients. We increased the acquisition time from 4 to 30 min to improve counting statistics.

While keeping the patients in exactly the same position, ^{81m}Kr ventilation scintigraphy (in the first 7 patients) or conventional intravenous ^{99m}Tc-macroaggregated albumin perfusion scintigraphy (in the last 15 patients) was subsequently performed. Nine patients (1–6, 11, 15, 19) underwent both ventilation and perfusion scintigraphy. We observed no complications related to the scintigraphic examinations.

Radiolabeling Stability

We reduced the number of tracer particles to approximately 10%–20% of the amount routinely used for pulmonary scintigraphy to minimize a theoretical risk of clinically significant bronchial arteriolar occlusion. The added activity of ^{99m}Tc per molecule of macroaggregated albumin was 2.4 times higher than that recommended by the manufacturer to obtain an adequate counting rate.

Quality control, particularly for autoradiolysis, was done by thin-layer chromatography. Measurements expressed as the percentage of ^{99m}Tc-macroaggregated albumin/free ^{99m}Tc-pertechnetate in the Technescan Lyo macroaggregated albumin preparation and the percentage of ^{99m}Tc-HAM/free pertechnetate in the TCK-5 CIS Bio International-preparation, respectively, showed 0.6%–1.4% free pertechnetate in the Technescan Lyo macroaggregated albumin preparation, and 0.6% free pertechnetate in the TCK-5 CIS preparation for patient 22, 105 min after the preparation.

However, in the TCK-5 CIS preparation used for patient 21 we observed 8.2% free pertechnetate after 5 min. In patient 22, there was only 0.6% free pertechnetate after 5 min, a result more consistent with the previous controls. The reason for the different labeling efficiencies in the preparations for patients 21 and 22 is unknown.

Visual Data Analysis

All images were calibrated to a hot iron color scale (dark = few counts/pixel, light = many counts/pixel). The upper limit of the scale was adjusted to give optimal presentation of the radioactive distribution and intensity, whereas the lower limit was set to 0 counts/pixel = black.

Figure 2A shows a typical bronchial artery perfusion scintigraphy image and Figure 2B the corresponding conventional pulmonary perfusion scintigraphy. To facilitate orientation, the outline of the lungs and main anatomic structures has been superimposed on the bronchial artery perfusion scintigraphy image. All scintigraphic images and the distribution and the pattern of the bronchial artery activity in relation to the main anatomic landmarks and to the mammary-bronchial arteriographic classification were analyzed and described by the same observer.

Quantitative Data Analysis

To quantify the distribution of the bronchial perfusion, each hemithorax was outlined by adjustable rectangular regions of interest (ROIs) on the Starcam 3200 computer screen. ROIs were approximated at the midline of the chest. After correcting for background activity, an epigastric ROI was drawn just caudal to the lungs but cranial to the low activity usually present in the stomach.

Counts from both hemithoracic regions were measured and expressed as percentages of total thoracic activity. From each hemithorax the scintigraphic activity was compared with the arteriographic classification described above.

The peripheral parts of the lungs in the bronchial scintigraphic studies were evaluated by outlining the area between the 5% and 25% isocontour lines, from the bottom of the phrenico-costal angle to the apices of the lungs, in the ventilation or perfusion studies. The areas outlined by this procedure were then copied and superimposed as templates onto the bronchial perfusion images from which the radioactivities within these ROIs were measured. The method is illustrated in Figure 3. The results were expressed as "template-area-to-background-area ratio" of radioactivity (Table 1). This technique was used to obtain a standardized and unbiased, albeit arbitrary, definition of the peripheral pulmonary regions.

No differences were observed between the isocontour curves of the pulmonary perfusion scintigraphies and the ventilation scintigraphies in patients who had both studies performed (n = 9).

RESULTS

All patients had normal or nearly normal intravenous pulmonary perfusion and/or ventilation scintigraphic images in the anterior projection. The images of the bronchial artery perfusion scintigraphic studies of all 22 patients are shown in Figure 4. Quantitative analysis of right/left distribution of activity is shown in Table 1.

Bronchial Artery Perfusion Images

Complete BAR and Incomplete BAR. The typical finding was an "H-shape" with the center of the "H" placed around the carinal area and near the pericardium, while the arms of the H were placed in the upper and lower lung lobes (Fig. 4). In all studies, activity in the central as well as in the peripheral parts of the lungs was definitely higher than the background activity. In most scintigraphic images, small areas of increased activity (hot spots) were recognized, resulting in a patchy pattern around the H shape. In many patients (4, 5, 9, 10, 12, 18, 19 and 21), focal accumulations appeared in the left upper arm of the H, corresponding to the internal mammary artery graft. Variable but usually low uptake was observed in the thyroid gland and the stomach, probably due to some free pertechnetate. In one patient (22), activity was observed corresponding to a left intercostal

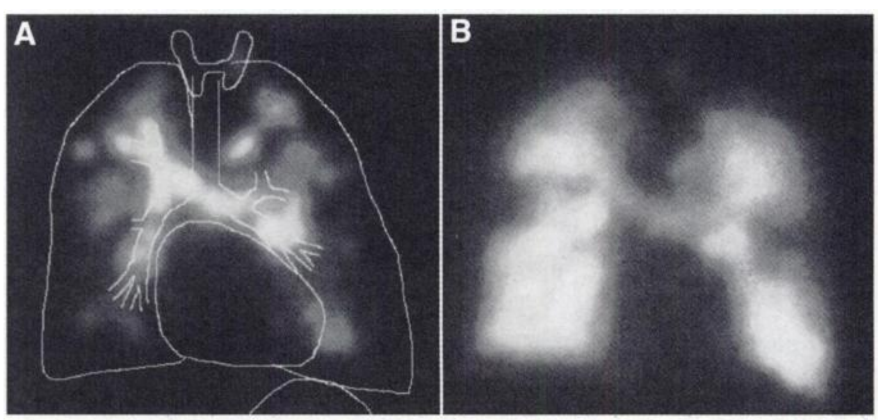

FIGURE 2. (A) Bronchial artery scintigram of patient 8, with superimposed schematic outline of major thoracic structures. (B) Pulmonary perfusion scintigram of same patient, with preceding bronchial artery scintigram.

artery seen on the arteriography to leave the internal mammary artery before the bronchial artery anastomosis.

Poor BAR. According to the bronchial arteriographies, in 2 patients, only a few small central thoracic bronchial arteries were successfully revascularized. Scintigraphy showed the activity to be largely confined to small areas corresponding to the mammary artery and these few central bronchial arteries.

Time After Transplantation. There were no visual or quantitative differences between bronchial artery scintigrams of patients examined 1 mo after transplantation and those of patients examined 2 y after transplantation.

Quantitative Analysis

The percentage distribution of right-to-left activities ranged from 14/86 to 50/50 (Table 1). In only one patient (13) was observed activity higher on the right side than on the left.

The usual high activity in the left hemithorax was probably caused by activity in the internal mammary artery conduit and in the small vessels from the conduit to the left side of the pericardium. In the mammary-bronchial arteriographies, these left-sided pericardial vessels leaving the conduit before the mammary-bronchial artery anastomosis were found in all 22 patients.

As mentioned above, arteriography in patient 22 revealed an intercostal artery leaving the proximal part of the internal mammary artery. In all patients, activity in the peripheral ROIs exceeded background activity (median ratio peripheral ROI-to-background activity, 2.0; range, 1.1–38.0), indicating that bronchial artery blood supply reached even the most peripheral parts of the lungs (Table 1). The activity of the right peripheral ROIs, from the 2 patients with arteriographically poor BAR, was 1.7 and 11 times the background activity, although, due to contrast, scaling and contrast settings this is not clearly visible in Figure 4.

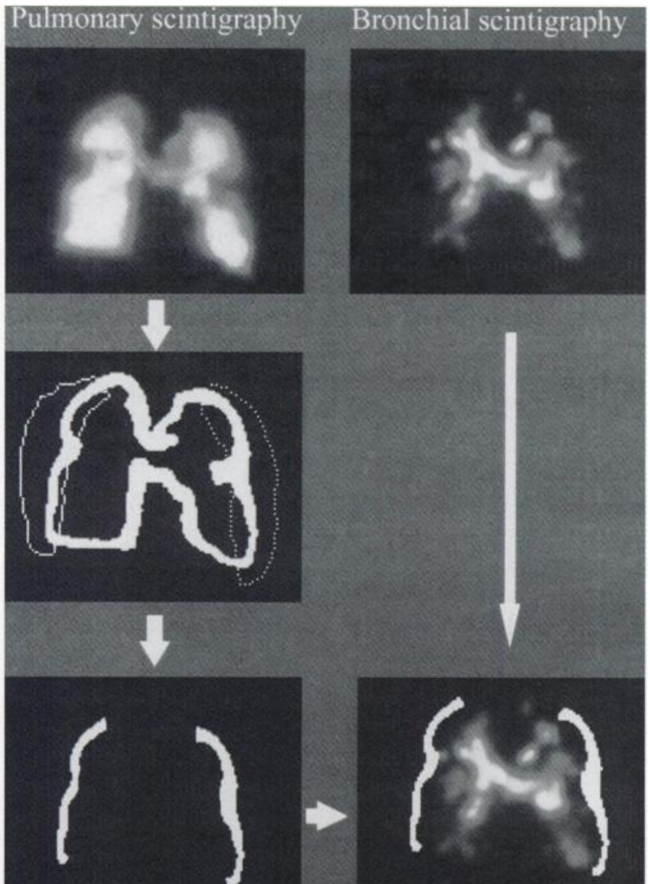

FIGURE 3. Peripheral ROIs were defined by outlining 5%–25% isoactivity count zones from intravenous pulmonary perfusion or ventilation images. Peripheral parts of clichés were cut (dotted lines) and automatically transferred via computer to bronchial artery perfusion image. Activity within this ROI was then measured from bronchial artery perfusion study.

TABLE 1
Relative Count Rates From Bronchial Artery Perfusion Scintigraphy In Pulmonary Regions of Interest (ROIs) in Relation to Arteriographic Classification of Revascularization Success

Patient no.	Right lung/ left lung % activity	Right ROI activity / background activity	Left ROI activity / background activity
Complete BAR			
2	37/63	1.2	1.1
3	35/65	1.3	1.3
4	42/58	2.1	1.4
5	39/61	1.4	1.4
6	36/64	1.3	1.7
7	35/65	2.0	3.3
8	50/50	1.2	1.3
10	39/61	1.1	1.3
11	42/58	4.0	5.5
12	27/73	2.9	6.4
13	60/40	1.8	1.7
14	38/62	1.1	1.5
17	37/63	2.2	3.7
18	18/82	3.1	9.5
19	25/75	3.0	8.5
20	41/59	2.9	2.7
21	14/86	1.2	2.3
22	18/82	1.4	16.7*
Median	35/65	1.6	2.0
Range	14–60/40–86	1.1–4.0	1.1–16.7
Incomplete bilateral BAR			
1†	33/67	1.5	1.5
9†	16/84	1.6	2.3
Poor BAR			
15	6/94	11.0‡	38.0‡
16	3/97	1.7	10.1‡

*A left intercostal artery was observed leaving the mammary artery proximal to the bronchial artery anastomosis.

†These patients both have transmediastinal collaterals from the right to the left side.

‡Abnormally high peripheral ROI activity-to-background activity ratio.

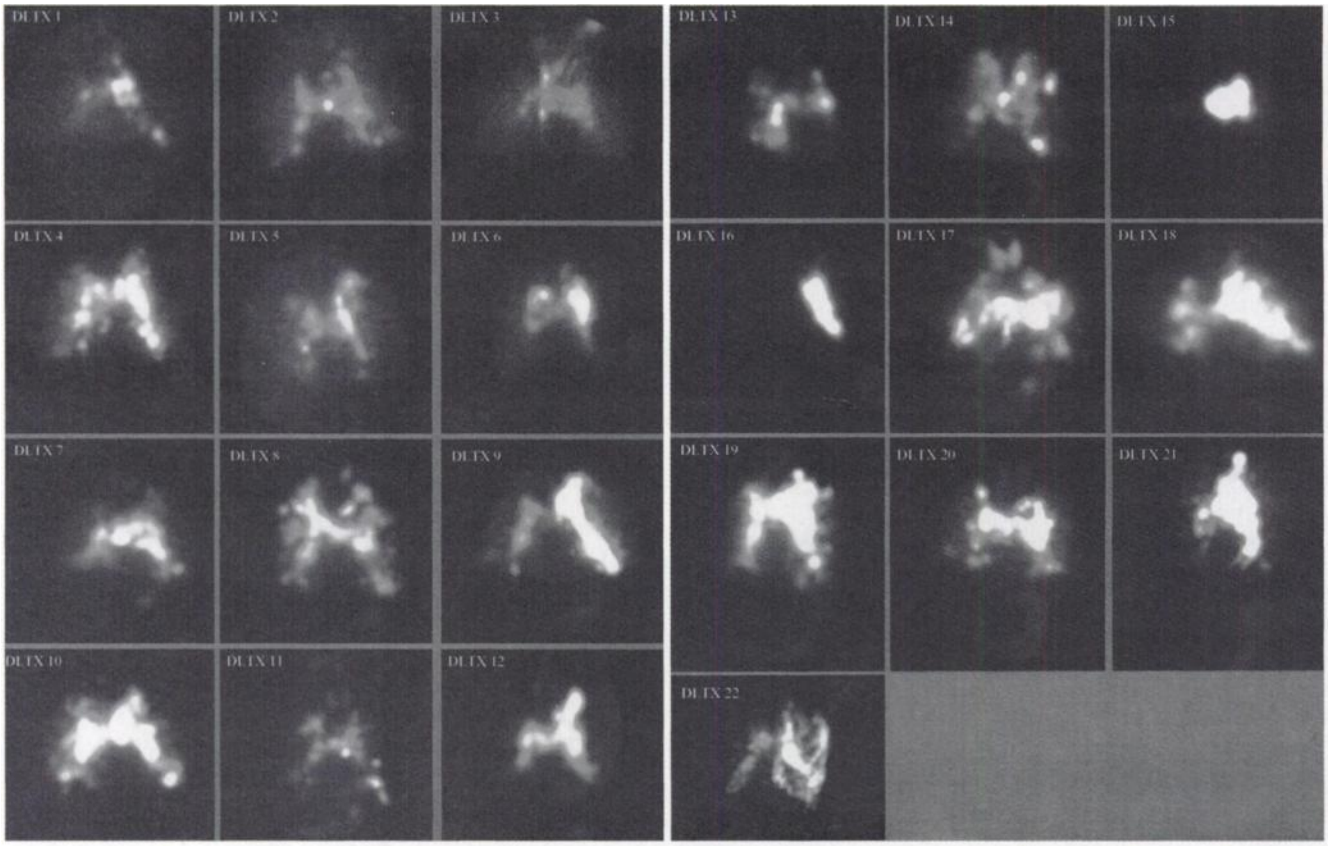

FIGURE 4. Bronchial artery perfusion images, patients 1–22. Patients 15 and 16 have poor BAR, and most of activity is confined to small areas corresponding to internal mammary artery used as conduit and few revascularized bronchial arteries located in central thorax. In patients 21 and 22 ^{99m}Tc-HAM was used. These scintigrams do not differ from those performed using ^{99m}Tc-macroaggregated albumin, with exception of area in patient 22 with increased activity in left intercostal artery, leaving internal mammary artery before bronchial artery anastomosis.

DISCUSSION

Normal bronchial arterial blood flow is supposed to be only a small percentage of the cardiac output but may play an important role for nutrition of the airways and the lung parenchyma. To our knowledge, this study is the first to visualize the distribution of perfusion to the lungs from the bronchial arteries. The study was performed in transplanted and denervated lungs, but it seems reasonable to believe that the flow distribution observed in our patients with complete BAR is comparable to that of healthy individuals. From the bronchial scintigraphic images (Fig. 4), it was evident that although the major part of the perfusion supplied centrally located thoracic structures, some of the scintigraphic tracer reached the most peripheral parts of the lungs. The finding of activities higher than background in all peripheral pulmonary regions indicates that at least some oxygenated blood from the bronchial arteries reached even the most peripheral parts of the lungs. This opens the possibility that ciliary function, mucus production, lymph node function and the general inflammatory response in infection and rejection may depend on bronchial artery blood flow in unrecognized ways.

When organ procurement is performed using our current technique for BAR (*1*), the donor is heparinized, and the pulmonary circulation is flushed with a modified Euro-Collins (Fresenius AG, Hamburg, Germany), but no special attempts are made to flush the bronchial arteries with the preservation fluid. The results of this study demonstrate that the bronchial artery circulation is well preserved after transplantation.

Precapillary collaterals between the bronchial arteries and pulmonary alveolar microvessels ("bronchopulmonary arteries") have been demonstrated earlier (*8,9*). These arterioles measure 50–400 μm (*9*). The recorded peripheral activity could derive from tracer reaching these areas directly through bronchial arteries or indirectly via bronchopulmonary arteries and then via the pulmonary arterial network. In this context it is interesting to note that both patients with poor BAR (15, right and left ROIs; 16, left ROI) had higher peripheral area-to-background-area activity ratios than any other patient (Table 1). The explanation may be related to an abnormal bronchial artery network in these patients, with a high percentage of the tracer draining to the bronchopulmonary arteries and into the pulmonary circulation, to be trapped in precapillary pulmonary vessels evenly distributed throughout the lung parenchyma, including the peripheral ROIs.

As seen from Table 1, all our double lung transplanted patients, except patient 13, had a higher counting rate in the left ROI than in the right ROI. This was probably caused by residual pericardial branches leaving the internal mammary artery before the anastomosis. The increased activity in the upper left hemithorax seen in several patients probably reflects tracer trapped in small branches including the vasa vasorum of the internal mammary artery.

We assume that the H-shaped activity found in all bronchial artery scintigraphic studies of patients with arteriographically complete or partial bilateral BAR reflects blood flow to the main bronchi and associated peribronchial tissue including lymph nodes. Studies in human cadavers (*10*) suggested that the bronchial artery network also supplies the visceral pleura, the walls of the pulmonary arteries and veins, hilar and mediastinal lymph nodes and the posterior part of the pericardium. Furthermore, the bronchial arteries normally supply branches to the esophagus, vagal and symphatic nerves and the myocardium, but these branches are cut during organ harvesting and preparation.

A distinctive finding in most of the studies was the hot-spot pattern seen in close proximity to the central H shape. These small focal accumulations could represent parabronchial lymph nodes or, alternatively, localized areas of current or previous inflammation or infection. In sheep with experimentally induced pulmonary abscesses, it has been demonstrated that the bronchial artery system provides the only blood supply to the membranes around the lung abscesses (*11*). An incidence of lung abscesses of 2%–5% after lung transplantation has been reported (*12,13*). Lung abscesses have not been observed in any of our 70 lung transplanted patients with arteriographically successful BAR (54 en bloc double lung transplantations, 10 single lung transplantations and 6 heart-lung transplantations) (Nørgaard MA, et al., unpublished data, January, 1998). Nor have we seen bronchomalacia in any patient with successful BAR, whereas other centers have reported this complication in 7%–50% of their transplant patients (*14–16*). The absence of these clinical complications in our en bloc double lung transplanted patients with successful BAR, in combination with the widespread distribution of bronchial artery flow, suggests that revascularization of the bronchial arterial system in lung transplantation may play an important role for the clinical outcome.

CONCLUSION

With injection through an arteriographic catheter and gamma camera imaging in the anterior projection, the distribution of the bronchial arterial system perfusion has been visualized in double lung transplantation patients with successful bronchial artery revascularization. The major part of the perfusion supplies the central thoracic structures, but the most peripheral parts of the lungs also receive some of this blood supply. This distribution pattern does not differ between patients studied 1 mo or 2 y after transplantation. The image of the bronchial arterial perfusion in the successfully revascularized double lung transplantation patients is probably similar to that of healthy subjects.

ACKNOWLEDGMENT

This study was performed with financial support from The Danish Research Council.

REFERENCES

1. Pettersson G, Nørgaard MA, Arendrup H, et al. Direct bronchial artery revascularization and en-bloc double lung transplantation—surgical techniques and early outcome. *J Heart Lung Transplant.* 1997;16:320–333.
2. Couraud L, Baudet E, Martigne C, et al. Bronchial revascularization in double-lung transplantation: a series of 8 patients. Bordeaux Lung and Heart-Lung Transplant Group. *Ann Thorac Surg.* 1992;53:88–94.
3. Daly RC, Tadjkarimi S, Khaghani A, Banner NR, Yacoub MH. Successful double-lung transplantation with direct bronchial artery revascularization. *Ann Thorac Surg.* 1993;56:885–892.
4. Pettersson G, Arendrup H, Mortensen SA, et al. Early experience of double-lung transplantation with bronchial artery revascularization using mammary artery. *Eur J Cardiothorac Surg.* 1994;8:520–524.
5. Svendsen UG, Nørgaard MA, Andersen CB, et al. Clinical results after en bloc double lung transplantation with direct bronchial revascularization [in Danish]. *Ugeskrift For Læger.* 1996;23(159):3592–3597.
6. Nørgaard MA, Efsen F, Arendrup H, Olsen PS, Svendsen UG, Pettersson G. Surgical and arteriographic results of bronchial artery revascularization in lung and heart lung transplantation. *J Heart Lung Transplant.* 1997;16:302–312.
7. Nørgaard MA, Efsen F, Andersen CB, Svendsen UG, Pettersson G. Medium-term patency and anatomical changes after direct bronchial artery revascularization in lung and heart-lung transplantation with the internal thoracic artery conduit. *J Thorac Cardiovas Surg.* 1997;114:326–331.
8. Wagenvoort CA, Wagenvoort N. Arterial anastomoses, bronchopulmonary arteries, and pulmobronchial arteries in perinatal lungs. *Lab Invest.* 1967;16:13–24.
9. Tobin CE. The bronchial arteries and their connections with other vessels in the human lung. *Surg Gynecol Obstet.* 1952;95:741–750.
10. Moberg A. Anastomoses between extracardiac vessels and coronary arteries. 3. Microangiographic appearance. *Acta Radiol Diagn Stockh.* 1968;7:33–47.
11. Charan NB, Turk GM, Dhand R. The role of bronchial circulation in lung abscess. *Am Rev Respir Dis.* 1985;131:121–124.
12. End A, Helbich T, Wisser W, Dekan G, Klepetko W. The pulmonary nodule after lung transplantation. Cause and outcome. *Chest.* 1995;107:1317–1322.
13. Snell GI, de Hoyos A, Krajden M, Winton T, Maurer JR. Pseudomonas cepacia in lung transplant recipients with cystic fibrosis. *Chest.* 1993;103:466–471.
14. Egan TM, Westerman JH, Lambert CJ Jr, et al. Isolated lung transplantation for end-stage lung disease: a viable therapy. *Ann Thorac Surg.* 1992;53:590–595.
15. Novick RJ, Ahmad D, Menkis AH, et al. The importance of acquired diffuse bronchomalacia in heart-lung transplant recipients with obliterative bronchiolitis. *J Thorac Cardiovasc Surg.* 1991;101:643–648.
16. Noirclerc MJ, Metras D, Vaillant A, et al. Bilateral bronchial anastomosis in double lung and heart-lung transplantations. *Eur J Cardiothorac Surg* 1990;4:314–317.