Human bronchial artery blood flow after lung Tx with direct bronchial artery revascularization

MARTIN A. NØRGAARD,1 JENS D. HOVE,2 FRITZ EFSEN,3 KARI SAUNAMÄKI,2 BIRGER HESSE,4 AND GÖSTA PETTERSSON1
Departments of 1Cardiothoracic Surgery, 2Cardiology, 3Radiology, and 4Clinical Physiology and Nuclear Medicine, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark

Nørgaard, Martin A., Jens D. Hove, Fritz Efsen, Kari Saunamäki, Birger Hesse, and Gösta Pettersson. Human bronchial artery blood flow after lung Tx with direct bronchial artery revascularization. J. Appl. Physiol. 87(3): 1234–1239, 1999.—The inaccuracy of measuring human bronchial artery blood flow has previously been considerable. En bloc double-lung transplantation with bronchial artery revascularization (BAR) using a single conduit offers the unique opportunity of direct measurement of the total bronchial artery blood flow. In eight en bloc double-lung-transplanted patients with complete BAR, the basal blood flow was measured by using a 0.014-in. Doppler guide wire and arteriography. The average peak velocity in the conduit was 12–73 cm/s [± 2.1 (SD) cm/s], and the conduit diameter was 1.7–3.1 mm [± 0.10 (SD) mm], giving individual basal flow values between 19 and 67 ml/min [± 5 (SD) ml/min], or 0.2–1.9% of estimated cardiac output. In three patients basal measurements were followed by injection of nitroglycerin and verapamil into the conduit. This increased the bronchial artery flow to 121–262% of basal values (31–89 ml/min). The measured values appear more physiologically plausible than previous bronchial artery blood flow measurements in humans.

transplantation; FloWire; Doppler; arteriography

vention, all based on the assumption that the bronchial artery blood flow originates from a common trunk that is easily accessible surgically. In humans, however, the anatomy of the bronchial arteries is quite variable and difficult to gain access to as they leave the thoracic descending aorta in numbers of between one and six (22). Therefore, only a few studies have been published on bronchial artery blood flow in humans. In most of the previously published studies of bronchial artery blood flow in humans, Fick’s principle was applied (13, 28, 30, 31). The inaccuracy of this method has been considerable.

None of the previously published studies have included direct measurements of the bronchial artery blood flow.

As the bronchial arteries of the patients in this study were supplied by only one conduit (the left internal mammary artery), we had the opportunity of measuring total bronchial artery blood flow. The purpose of the present study was to measure the bronchial artery blood flow in patients who had received en bloc DLTx with complete BAR and to examine whether the bronchial artery blood flow could be increased by pharmacological vasodilators.

Materials and Methods

We previously published our method for performing DLTx with BAR, which includes anastomosing of the left internal mammary artery to as many bronchial artery orifices as possible in the donor descending aorta that was harvested with the lung bloc (37).

Cine mammary-bronchial arteriography by using the Seldinger technique was routinely performed ~1 mo after the transplantation to evaluate the result of the revascularization. Mammary-bronchial arteriography was performed by introducing the tip of a 6F catheter (Cordis IM, no. 532 623) into the origin of the mammary artery under fluoroscopic control. Using hand injection of contrast medium (Omnipaque, 350 mg/ml), cine runs were carried out in the anteroposterior, lateral, 45° left anterior oblique, and 45° right anterior oblique projections. All cine films have been carefully studied, and the result of BAR has been classified according to our previously published classification system (33). Routinely, the patency of the BAR has been controlled after 2 yr by another mammary-bronchial arteriography.

Eight DLTx patients scheduled for mammary-bronchial arteriography were included in this study. Only patients who had arteriographically complete BAR (i.e., at least 1 bronchial artery ramus for each lung lobe) were included in the study. Two patients (patients 3 and 5) were examined 1 mo...
after DLTx, whereas the rest of the patients were examined 2 yr after DLTx.

After completing the arteriography, the patients were heparinized (5,000 IU), and a Doppler guide wire (FloWire, J-tip, soft, 0.014 in.) was introduced through the 6F arteriographic catheter and connected to a FloMap computer (Cardiometrics). Because pericardial vessels were usually found to branch from the mammary artery proximal to the internal mammary artery-bronchial artery anastomosis, the tip of the FloWire was advanced beyond these branches until it was just proximal to the mammary-bronchial artery anastomosis (Fig. 1, A and B). In this position the total blood flow through the internal mammary artery passed the FloWire before entering the bronchial arteries. With the FloWire kept in this position, the arteriographic catheter was carefully retracted into the subclavian artery, to avoid obstruction of the flow through the internal mammary artery orifice. Four to eight flow measurements were performed. Between the first and the last measurements the catheter was retracted slightly to establish whether this would change the measured flow velocity. The time interval from completing the arteriography to performing the first flow measurement was 2–8 min.

In the last three patients the arteriographic catheter was repositioned in the internal mammary artery ostium after the first five measurements had been completed in the same location, and a 1-ml mixture of 0.2 mg/ml nitroglycerin (glycerylnitrate) and 0.2 mg/ml verapamil was injected through the catheter, to selectively dilate the mammary artery and bronchial artery network without introducing systemic effects. Immediately after injection the arteriographic catheter was retracted into the subclavian artery and five more flow measurements were completed, as fast as possible; 1 min later a last flow measurement was performed. The interval from retraction of the arteriographic catheter until the first flow measurement was <1 min. All FloWire positions were documented radiographically.

During the study, the routine radiographic technique was changed, so that the first five patient examinations were recorded by using cine film, whereas the last three patients were examined by using digital imaging (Philips Integris BV 3000). In all cases the arteriographic catheter and the internal mammary artery were focused in the same frame to avoid pincushion distortion. The diameter of the internal mammary artery at the level of the FloWire J-tip was determined by using the 6F arteriographic catheter as a reference. In the cine arteriographies this could be established, corresponding to each guide wire position, by five repeated computer caliper measurements performed after digitizing and magnification (×4,000) of the arteriographic cine images. The magnification factor was calculated after five repeated computer caliper measurements of the arteriographic catheter, with the knowledge that the true diameter of this was 1.91 mm. In the digital images the measurements could be established automatically on the Philips Integris BV 3000 computer, which was calibrated to use the X-ray-contrast, medium-filled catheter for reference (15). On the assumption that the wall of the internal mammary artery was circular at the level of measurement, the flow volume could be calculated from the average peak velocity (APV) and the vessel diameter

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\text{B Bronchial artery flow} = \frac{\text{observed IMA diameter}}{2} \times \pi \times \text{APV} \times 0.5
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On the assumption of a time-averaged parabolic velocity profile across the internal mammary artery, the mean flow velocity was considered to be 0.5 × APV as previously described by Doucette et al. (16).

The SD for the flow values was calculated from the SD and the mean for repeated measurements of the catheter diameter, the internal mammary artery diameter, and the APV measurements, by using the delta method (39). The coefficient of variation was calculated as flow SD divided by flow mean for each set of measurements.

The patients' height, weight, body mass index, surface area, forced inspiratory volume in 1 s (FEV1), forced vital capacity, and total lung capacity were established and used in the statistical analyses below. As the ethical committee does not allow invasive measuring methods for cardiac output measurement for research purposes, the cardiac output was calculated from a cardiac index estimated to be 2.5–4.5 l·min⁻¹·m⁻² (26).

Ethics. The patients were informed orally and in writing about the study and signed an informed consent document. The study was approved by the local ethical committee (j. no. KF 01–344/96 and KF 01–104/97).

Statistical analysis. For testing of correlations between bronchial artery flow and other patient data, Spearman's correlation analysis was applied.

RESULTS

The internal mammary artery diameter among patients varied from 1.7 to 3.1 mm. Repeated measurements from the digitized cine arteriographies established the internal mammary artery diameter with a mean (SD) of 0.10 mm (SD range: 0.06–0.14 mm).

Repeated measurements from the same images established the arteriographic catheter diameter with a mean (SD) of 0.064 mm (SD range: 0.001–0.088 mm).

The APV varied between 12 and 73 cm/s. Repeated APV measurements resulted in a mean (SD) of 2.1 cm/s (SD range: 0.71–4.7 cm/s).

Bronchial artery blood flow values are listed in Table 1 together with estimated cardiac output and bronchial artery blood flow as a percentage of the estimated cardiac output. In the last three patients the bronchial artery flow values after injection of glycerylnitrate and verapamil are listed together with the percent flow increases.

The increase in APV after injection of glycerylnitrate and verapamil was of short duration. Table 1 shows the flow values before injection, just after vasodilation, and 1 min later. In all three patients injection of glycerylnitrate and verapamil resulted in an increase in flow velocity higher than two SDs.

Knowing that X-ray contrast medium may dilate the bronchial artery bed, we injected a bolus of X-ray contrast medium into the internal mammary artery (in 1 patient) to study whether this would increase the flow. Even though the contrast medium increased the flow by 60%, this effect lasted only very briefly. After <1 min the flow was back to the baseline value. As it took a minimum of 2 min, usually longer, to position the FloWire, we suppose the influence of the X-ray contrast medium to be negligible.

Bronchial artery blood flow was not correlated (Spearman's test) with patient height, weight, body mass
Fig. 1. A: thin arrow, 6-Fr arteriographic catheter; intermediate-size arrow, internal mammary artery conduit; thick arrow, internal mammary artery-bronchial artery anastomosis. B: *, Arrow: tip of Doppler FloWire in internal mammary artery conduit just proximal to anastomosis.
FloWire was compared with the cross-sectional area of the blood flow, the cross-sectional area of the artery, and reduced lung function in patients with bronchiectasia, chronic obstructive pulmonary disease, and pulmonary avascular lobectomy. Although there seemed to be an inverse relationship between high bronchial artery blood flow and reduced lung function in patients 3 and 7, this correlation was not significant.

To examine whether the FloWire might cause obstruction of the blood flow, the cross-sectional area of the FloWire was compared with the cross-sectional area of the smallest internal mammary artery found (3.2 mm²). The FloWire cross-sectional area was 0.1 mm², which was only 4% of the smallest internal mammary artery cross-sectional area.

Because the FloWire measurements must be influenced by turbulent flow, the Reynolds number was calculated for each set of measurements (using the absolute peak velocities, not the APVs, which are somewhat smaller), resulting in Reynolds numbers between 44 and 125.

The mean coefficient of variation, calculated as previously described, was ±14% (SE 1.3%).

**DISCUSSION**

In experimental animals, a large variety of methods has been used to measure the bronchial artery blood flow. The simplest but rather nonphysiological method used has been direct “cup-flow” (11). Probably more physiological flow measurements have been obtained by tracing of microspheres labeled with color or radioactive isotopes (6, 21, 29) or by using a variety of perivascular electromagnetic (1, 24, 25, 35) and ultrasonic transit-time flow probes (2, 9, 10, 19, 27, 36, 38), videodilution techniques based on Fick’s principle (23), a rotameter in the bronchial artery bloodstream (20), or a pressure-controlled pump, supplying blood flow to the bronchial artery trunk (as the only source), that maintains the same pressure in the bronchial artery trunk as in the aorta (12, 41). Most of these methods may reliably determine bronchial artery flow values in experimental animals, but, unfortunately, all are based on the assumption that the bronchial artery blood flow derives from one common trunk, which is easily accessible surgically. However, the anatomy of the human bronchial arteries is quite variable (17, 33). From a catheterization point of view, the bronchial arteries are awkwardly positioned, as they leave the descending thoracic aorta, and are not easily accessible for surgery nor for direct flow measurements because the number of arteries is variable (22). Therefore, only a few studies on bronchial artery blood flow in humans have been published. In most previously published studies on bronchial artery blood flow in humans, Fick’s principle has been applied by cannulating the pulmonary trunk and the left atrium (13, 28, 30, 31). In individuals without lung disease (a total of 17 individuals) an estimated aortopulmonary collateral flow of up to 560 ml/min (8.2% of cardiac output) has been found. In one study, which included nine healthy individuals and used the dye-dilution technique (18), a wide range of flow values, including even negative values, were reported. The inaccuracy of these techniques was considerable, as reflected by the fact that the bronchial artery blood flow in patients with various lung diseases (tuberculosis, bronchiectasis, chronic obstructive pulmonary disease, pulmonary cancer, silicosis, pulmonary abscess, and so on) was estimated to range from −12 to 55% of cardiac output, indicating a methodological problem.

One previous study measured the blood flow to the left ventricle in 40 patients on extracorporeal circulation who were undergoing coronary artery bypass surgery (3). Flow values of 140 ± 182 (SD) ml/min (3.23–4.15% of the pump flow) were recorded. During the same conditions, Deal et al. (14) found the flow to be 3.8 ± 2.7% of the pump flow. Although measurements were made under nonphysiological conditions, they appear more reliable than previous ones using Fick’s principle.

Compared with previous human studies the present study model and method allowed us to determine bronchial artery flow levels in transplanted lungs under more physiological conditions with good reproducibility.

There are limitations to the accuracy of this method that are related to both the inaccuracies in the determination of the vessel diameter and the flow velocity. This resulted in a mean coefficient of variation of ±16%. The 0.5 factor used to correct for the parabolic velocity profile across the internal mammary artery, as described by Doucette et al. (16), has been our best estimate for this correction.

Because the FloWire would only occupy −4% of the internal mammary artery cross-sectional area, it should not have any obstructive effect on the flow. The Reynolds numbers calculated were much lower than 2,000 (the lower border for turbulent flow), indicating that the average measured peak velocities should be reliable. In small vessels, as in the internal mammary artery, the position of the FloWire tip being in the...
center or along the vessel wall should not be important. Is the bronchial artery flow measured in transplanted lungs comparable to that in healthy individuals? Transplanted lungs are denervated, eliminating autonomic vasomotor control. Systemic effects of the transplantation, including the pharmacological treatment, appear probable. The fivefold interindividual variation found among bronchial artery flow values may reflect that, although arteriographically complete BAR was found in all patients, minor branches of the bronchial artery system might be occluded after the lungs were explanted from the donor, reducing bronchial artery flow. Furthermore, collaterals from pleural, mediastinal, and diaphragmatic adhesions, usually found at autopsy after lung transplantation, may further influence the flow, compared with that in healthy subjects.

In animal studies the bronchial arterial blood flow was found to be regulated by a number of physiological, pharmacological and environmental stimuli. Physiological factors found to increase the bronchial artery blood flow are hypercapnia (4), vagus nerve stimulation (8), and application of humoral factors like adrenaline, serotonin, and histamine (8, 12, 20, 23, 24). Corresponding with our findings, pharmacological substances like nitroglycerin, theophylline, acetylcholine (8), the β-agonist isoproterenol (9), and high-osmolality substances like hyperosmolar NaCl, dextrose, and X-ray contrast media (Omnipaque and Conray 66) (5) have been found to increase the flow.

The results from studies on the effects of hypoxia and decreased pulmonary artery blood flow have been variable and contradictory (1, 4, 6, 7, 21, 40). It has recently been hypothesized that endothelial nitric oxide (NO) production is an important pivot in the mechanism regulating bronchial artery flow. It has been found that NO increases bronchial artery blood flow (10), whereas administration of the NO synthase inhibitor Nω-nitro-L-arginine methyl ester (9, 10, 27) decreases the flow. The pharmacological dilatation used in the present study was not dependent on endothelial function or NO.

Even though the X-ray contrast medium may increase the blood flow, this effect is quite brief, and, as it took us a minimum of 2 min (usually longer) to position the FloWire, we assume that the influence of the X-ray contrast medium was negligible.

Bronchial artery blood flow measurements are technically easy to perform by the present method. Although the method may not be quite suitable for studying critically ill patients, it would be interesting to study whether the bronchial artery flow changes in response to rejection, infection, and other lung insults.

The high bronchial artery flow found in patients with reduced lung function may suggest that these parameters are correlated, although not statistically significant, in this small population. If reduced pulmonary function is the consequence of an ongoing inflammatory process in the lungs, the process could be the cause of increased bronchial artery flow. If this flow increase is of importance to the healing process, it represents a beneficial effect of BAR.

Conclusions. Direct bronchial artery flow measurements using a Doppler FloWire and the arteriographic technique in patients with en bloc DLTx with complete BAR have been performed. Bronchial artery flow values between 19 and 89 ml/min were measured, corresponding to ~0.2–1.9% of cardiac output. The bronchial artery flow increased after injection of vasodilators. Although the bronchial artery flow values showed a fivefold interindividual variation, the measured values appear physiologically plausible to a greater extent than previous bronchial artery blood flow measurements in humans.

Address for reprint requests and other correspondence: M. A. Nørgaard, Dept. of Cardiothoracic Surgery, RT, 2152, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark (E-mail: bar@rh.dk).

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