DIRECT BRONCHIAL ARTERY REVASCULARIZATION IN LUNG TRANSPLANTATION

SURGICAL, ANATOMICAL, PHYSIOLOGICAL, AND CLINICAL ASPECTS

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This thesis is based on the following publications

I G. Pettersson, M. A. Nørgaard, H. Arendrup, P. Brandenhoff, M. Helvind, F. Joyce, P. Stentoft, P. S. Olesen, J. J. Thiis, F. Efsen, S. A. Mortensen, and U. G. Svendsen. Direct bronchial artery revascularization and en bloc double lung transplantation - Surgical techniques and early outcome. J Heart Lung Transplant 1997;16:320-333.

II M. A. Nørgaard, F. Efsen, H. Arendrupp, P. S. Olsen, U. G. Svendsen, and G. Pettersson. Surgical and arteriographic results of bronchial artery revascularization in lung and heart lung transplantation. J Heart Lung Transplant 1997;16:302-312.

III M. A. Nørgaard, F. Efsen, C. B. Andersen, U. G. Svendsen, and G. Pettersson. 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 Cardiovasc Surg 1997;114:326-331.

IV M. A. Nørgaard, C. B. Andersen, and G Pettersson. Does bronchial artery revascularization influence results concerning bronchiolitis obliterans syndrome and/or obliterative bronchiolitis after lung transplantation ? Eur J Cardiothorac Surg 1998;14:311-318.

V M. A. Nørgaard, N. Gadsbøll, F. Efsen, B. Hesse, A. Rabøl, and G. Pettersson. Bronchial artery perfusion scintigraphy to assess bronchial artery blood flow after lung transplantation. J Nucl Med 1999;40:290-295.

VI M. A. Nørgaard, C. B. Andersen, and G. Pettersson. Airway epithelium of transplanted lungs with and without direct bronchial artery revascularization. Eur J Cardiothorac Surg 1999;15:37-44.

VII M. A. Nørgaard, J. Hove, F. Efsen, K. Saunamäki, B. Hesse, and G. Pettersson. Human bronchial artery blood flow after lung Tx with direct bronchial artery revascularization. J Appl Physiol 1999;87(3):1234-1239.

Foreword

I imagine that the greatest gift and ultimate challenge for a young geographer must be to be given the opportunity of exploring a white area on the map. Few such areas remain available in the world today. This situation is not unique for geographical science but seems to be identical for many scientific areas, and indeed for the medical sciences. Most areas have previously been explored, mapped, and analyzed to a degree where only the most ingenious scientists are still able to find even minor "blank spots on the map". It takes true innovation to discover new areas of considerable size where exploring is not only possible but truly needed.

I was first introduced to the area of direct bronchial artery revascularization in April 1994 when professor Gösta Pettersson suggested that I began to research this area. It was with great honor that I welcomed the opportunity to explore this "blank spot on the map", previously only visited by very few scientists.

Preparing for my voyage into this blank spot took more than a year, and when I finally entered the territory it was with great expectations and drive.

I soon realized that these kinds of voyages are not easily conducted. It is of vital importance soon to identify the possible errors and pitfalls, not only in the landscape, but just as important, also when choosing collaborators. Generally I was lucky to find the best collaborators one could wish for, and as our explorations commenced we tried to stay out of the scientific swamps and away from the areas where cannibals ruled.

Looking back at the results we have accomplished, I feel that what we have done has been to supply this area with a useful description of the infrastructure, but that much remains to be done by future researchers. I have no certain feeling about the future role of this area. It may be a source of inspiration and success, or it may sink into oblivion.

No matter what the future role of direct bronchial artery revascularization will be, I feel that the voyage has been worth everything, and that this has been just as, or maybe even more, important than reaching the places we decided to go to.

I wish to thank the people who have taken part in the scientific work and those who made it possible financially. The research was performed from July 1995 till December 1998 during my employment as a research associate at The Department of Cardiothoracic Surgery, Rigshospitalet (financed by The Danish Lung Transplantation Group,

1995-1996), during my employment as research associate (financed by The Danish Research Council, 1997), and finally along with my employment as a surgical trainee at Rigshospitalet (1997-1998).
The number of people to thank for their helpfulness and cooperation is large, and mentioning everyone by name would be pointless. I hope that everyone involved knows how thankful I am. However, a number of people deserve special thanks. First of all I wish to thank professor Gösta Pettersson for giving me the opportunity to perform the scientific work, assisting me both financially and practically, giving me theoretical feedback whenever needed, as well as supplying professional and friendly support. I wish to thank Dr. Fritz Efsen and The Department of Radiology for the flexible cooperation and willingness to try new approaches, when performing arteriographies, scintigraphies, and flow measurements, and when analyzing the data. Dr. Birger Hesse and The Department of Nuclear Medicine and Physiology, and cardiologist Dr. Niels Gadsbøll, deserve special thanks for their enthusiasm, commitment, support, and stringent approach. I thank Dr. Claus B. Andersen and The Department of Pathology for their friendly cooperation and support. I also thank the co-workers at The Department of Cardiology for their contributions. Finally I thank my wife Hanne for her substantial support through "the journey", which included the birth of our twins Sille and Mark (1998) whom I thank for happiness, optimism, and sometimes even sleep, permitting the conclusion of this journey.

Copenhagen November 1999 *Martin Agge Nørgaard*

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Abbreviations

BAR : Direct bronchial artery revascularization.
BLTx : Bilateral lung transplantation = sequential bilateral lung transplantation.
BOS : Bronchiolitis obliterans syndrome.
DLTx : En bloc double lung transplantation.
FEV_1 : Forced expiratory volume during the first second.
HLTx : Heart-lung transplantation.
ISHLT : International Society for Heart and Lung Transplantation.
LTx : Lung transplantation
OB : Obliterative bronchiolitis.
RICBA: Right intercostobronchial artery.
SLTx : Single lung transplantation.

Definitions

Bronchial artery:

After leaving the orifice in the descending aorta the systemic arteries for the airways and lungs are named bronchial arteries. Branches/collaterals may exist for the visceral pleura, the walls of the pulmonary arteries and veins, the mediastinum, the esophagus, mediastinal hilar and intrapulmonary lymph nodes, the pericardium, the vagal and sympathetic nerves, and the myocardium.

Bronchial artery trunk:

An artery that, after its origin from the aorta, divides into bronchial arteries for both lungs.

Bronchiolitis obliterans syndrome (BOS):

A clinical syndrome with irreversible loss of lung function following lung transplant defined by the International Society for Heart and Lung Transplantation (ISHLT) as an irreversible loss of FEV_1 to $\leq$ 80 % of postoperative baseline FEV_1 [1].

Obliterative bronchiolitis (OB):

An airway obstruction syndrome, defined by the histological changes in the distal small bronchi described by Paradis and co-workers [2]. Histologically OB includes submucosal and intraepithelial mononuclear cell infiltration, fibrous plaques in the airways narrowing / obstructing the airway lumen, and submucosal dense eosinophilic scar tissue that in some cases extends into the peribronchial tissue, producing atrophy or loss of airway smooth muscles, and centrilobular fibrosis.

Introduction

Normal lungs have a dual blood supply. The pulmonary arteries provide desaturated blood under low pressure, and the bronchial arteries provide oxygenated blood under systemic pressure. The logical way to re-establish normal nutritive arterial blood supply after lung transplantation (LTx) is by direct bronchial artery revascularization (BAR).

Already in 1950 Metras had suggested that the bronchial artery circulation could be important to LTx [3]. To pursue this theory Metras performed experimental single lung transplantation (SLTx) with direct bronchial revascularization in dogs.

In 1973 Haglin and co-workers [4] first performed human left-sided LTx with BAR, and subsequently a second LTx on the right side without BAR. The patient survived for 11 days. At autopsy the donor main bronchus wall on the revascularized left side was "vital", while on the non-revascularized right side all layers of the donor main bronchus showed necrosis.

When Veith and co-workers analyzed the early clinical cases of LTx reported in the literature, they found that only one out of the first 38 patients who had undergone lung or lobe transplantation survived for more than three weeks [5]. The single dominating cause of death was dehiscence of the bronchial anastomosis. The conclusion was that some protection or revascularization of the airways was necessary for successful LTx. The method developed and used by the Toronto Lung Transplant Group to protect the airway anastomosis in the first successful LTxs, single as well as en-bloc double (DLTx), was to wrap the anastomosis with omentum [6,7]. In experimental animals wrapping with omentum or with an internal mammary artery (IMA) pedicle produced submucosal vascular ingrowth and minimized anastomotic stenosis development after autotransplantation [8]. Introducing distal main bronchus anastomosis and "telescoping" Calhoon and co-workers [9] presented successful SLTx without anastomotic wrapping. At the Harefield Hospital in London, 36 patients undergoing SLTx were randomized to omental wrapping or no wrapping, and no differences in the incidence of bronchial anastomotic complications were found between the groups [10]. Today SLTx is performed at most centers with distal main bronchus anastomosis with or without "telescoping", but without anastomotic wrapping. Bronchial healing is good, and bronchial complications few.

The early Toronto double lung transplants were performed en bloc with a tracheal anastomosis wrapped with omentum [7]. This method of

DLTx was associated with a very high incidence of ischemic airway complications (8 of 13 patients), and the poor results inspired introduction of sequential bilateral lung transplantation (BLTx) [11,12] as well as re-investigation of the possibility of performing LTx with BAR [13,14].

The anatomy of the human bronchial arteries as they branch from the aorta was carefully studied by several investigators [15-19]. These, and anatomical [13,20] and experimental studies [21],[22-24] were the basis for the development of a clinical method for BAR. However, it was not until 1992 that the Xavier Arnozan Hospital, Bordeaux, France [14], reported the first clinical series of eight patients in whom DLTx had been performed with successful BAR.

When the Copenhagen lung transplant program was planned (1990-1992), BLTx was not yet proven effective, nor was SLTx widely accepted for patients with emphysema or pulmonary hypertension. Based on these arguments and the knowledge of the techniques for BAR used in Bordeaux and London, it was decided to include BAR in lung transplants in Copenhagen whenever possible. When the LTx program was introduced in Copenhagen, the worldwide experience of LTx with BAR included approximately 20 patients.

Since 1992, reports of DLTx with successful BAR have been published from Harefield Hospital, London, England [25] and Rigshospitalet, Copenhagen, Denmark [26,27]. In 1994 the Mayo Clinic, Rochester, Minnesota, USA [28],[29] reported SLTx and BLTx with BAR, and in 1997 Helsinki University Central Hospital, Finland [30], reported heart-lung transplantations (HLTx) with BAR, using an IMA or saphenous vein conduit.

SLTx and BLTx without BAR produce good early results, but the long-term results after LTx remain mediocre and leave room for further improvements of long-term survival, lung function, and quality of life. Although re-establishing normal lung blood supply with BAR has not been excluded as a positive prognostic factor (**Figure 1-3**), most lung transplant surgeons consider BAR too difficult and too unreliable to be performed clinically. In spite of this we have found it relevant to pursue LTx with BAR, and further to develop the surgical technique and study short- and long-term effects. The following presents and discusses our studies of the bronchial artery anatomy, the surgical method for BAR, the evaluation of the surgical results, as well as our studies of the clinical outcome and physiology after LTx with BAR. The lung transplant activity 1992-1998 at Rigshospitalet in Copenhagen is shown in **Figure 4**.

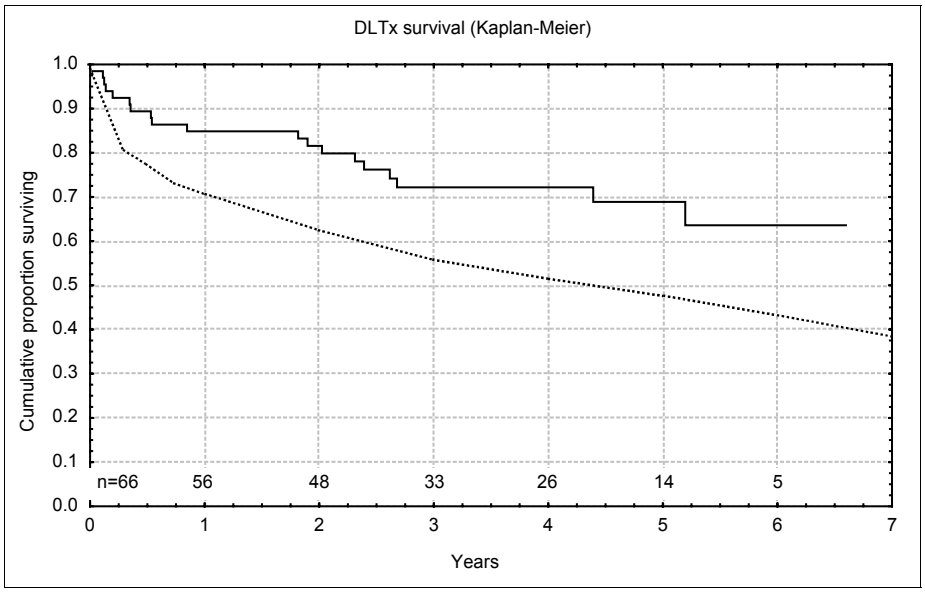

Figure 1 *Kaplan-Meier survival curves for DLTx with BAR from Copenhagen (line) vs. DLTx or BLTx from the ISHLT register (dashed).*

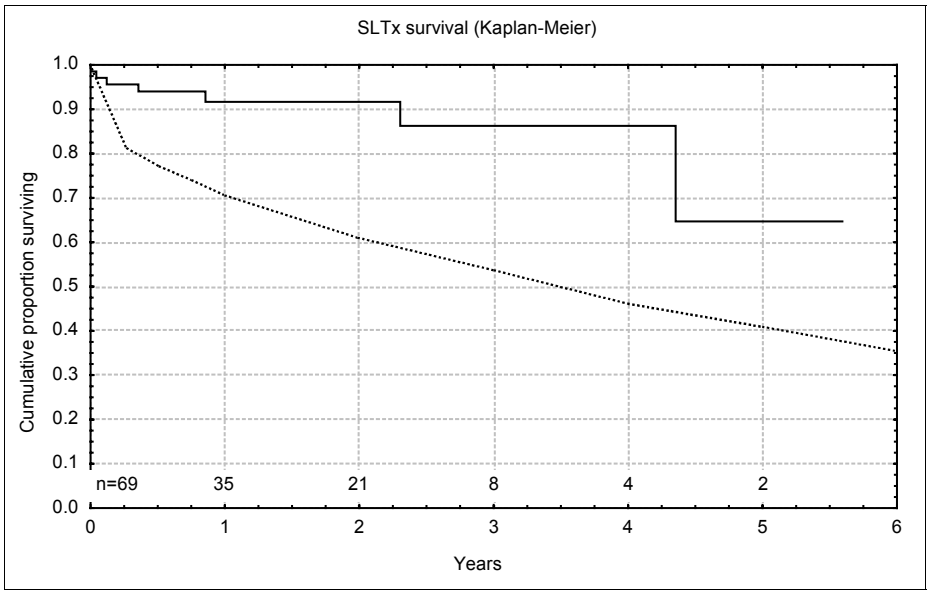

Figure 2 *Kaplan-Meier survival curves for SLTx with or without BAR from Copenhagen (line) vs. SLTx from the ISHLT register (dashed).*

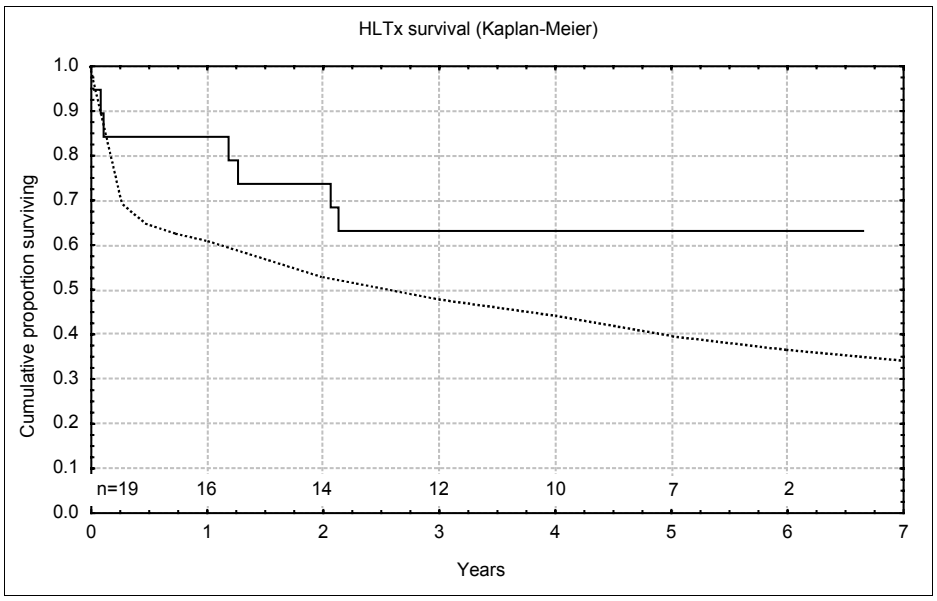

Figure 3 *Kaplan-Meier survival curves for HLTx with or without BAR from Copenhagen (line) vs. HLTx from the ISHLT register (dashed).*

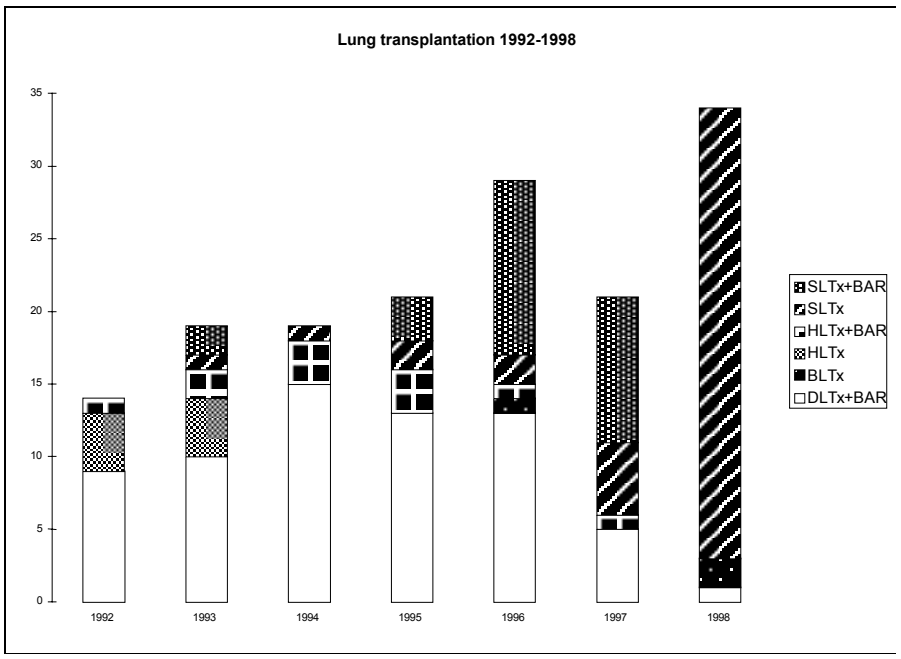

Figure 4 *The lung transplantation activity at Rigshospitalet in Copenhagen 1992-1998. After Gösta Pettersson left Rigshospitalet in 1998, LTx with BAR has not been performed.*

Aims

To develop a safe and dependable procedure for LTx with BAR.
To study the bronchial artery anatomy in the donor lungs.
To study the patency of BAR.
To study bronchial artery flow and flow distribution after LTx with BAR.
To study the effects of BAR on bronchial mucosa and ciliary beat frequency.
To study clinical outcome after LTx with BAR.

2.0 Normal anatomy of the bronchial arteries

The existence of small arteries from the systemic circulation to the lungs and airways of animals has been known since Galen [31].
The anatomy of the human bronchial arteries as they branch from the aorta has been carefully studied by several investigators [15-19].
The first large study of human bronchial artery anatomy was performed in 1948 by Cauldwell and co-workers [15] who dissected 150 cadavers. In 1965 Liebow [16] made corrosion casts of the bronchial arteries in 50 cadavers. Bronchial arteries originating in the descending aorta to supply both sides were always found, but there were numerous variations in their origin. In the aorta one or two arteries for each side were found in 40% and 42% of the cadavers, respectively. All other possible combinations of one to four arteries for each side were found, up to a total of six bronchial arteries. The commonest pattern was two left and one right bronchial artery, found in 20% and 41% of the cadavers, respectively.
Kasai and Chiba [18] performed dissections more recently in 40 cadavers and claimed two right and two left bronchial arteries (found in 25 % of individuals) to be the most common finding in their material.
A dissection study of the tracheobronchial blood supply in 20 human cadavers, and angiographic studies in 50 thoracic surgical patients [13], preceded the clinical introduction of BAR by Couraud and co-workers [14]. At a later stage these studies were expanded by the same group [32] by another 40 cadaver dissections, including contrast injections.
The results of all these studies and our own operative findings, describing the bronchial artery anatomy as the vessels originate and branch from the descending thoracic aorta, are summarized in **Table 1**.

Table 1

Author	Cauldwell et al. [15]	Liebow et al. [16]	Kasai et al. [18]	Schreine-makers et al. [20]	Dubrez et al. [13]	Carles et al. [32]	Nørgaard et al. II
n=	150	50	40	30	20	40	64
Method	Cadaver dissec-tions	Cadaver corrosion casts	Cadaver dissec-tions	Cadaver dissec-tions	Cadaver dissec-tions	Cadaver dissec-tions + contrast injection	Surgical identifica-tion
Number of BAs	1-5	1-6	2-10	1-6	1-3	2-4	1-4
RICBA	89 %	74%	85%	83%	76-95%	98%	65%
Separate right BA(s)	11 %	26%			15%	8%	8%
BA trunk(s)	27 %	84%	35%	23%	60%	50%	12%
Separate left BA(s)	73 %			93%	70%	95%	89%

The following types of bronchial arteries have been identified (**Figure 5**):

- The right intercostobronchial artery (RICBA) usually takes off from the aorta as the first right segmental artery. The RICBA is a common trunk for the first right intercostal artery and a right bronchial artery. Usually the first right segmental / RICBA-orifice attracts immediate attention when the descending aorta is opened because the orifice is usually larger than the other orifices. Within 1-2 cm from the aorta, behind the esophagus, the RICBA branches into the intercostal artery and a right bronchial artery (**Figure 6**).
- A subcarinal artery is defined by its direction directly towards the carina, and it is easily recognized by the location of its orifice in the aorta, which is proximal and medial to the first segmental artery. A subcarinal artery could be a distal tracheal ramus, a right bronchial artery, a bronchial artery trunk, or more seldom even a left bronchial artery.
- Separate right bronchial arteries have their course in front of the esophagus. The orifice is usually located in the area between the subcarinal artery and the first right segmental artery.
- Separate left bronchial arteries are highly variable in location, number, and size.
- A bronchial artery trunk can have as variable a location as the left bronchial arteries. It is defined by supplying bronchial arteries to both the right and the left side. More than one bronchial artery trunk may be present.

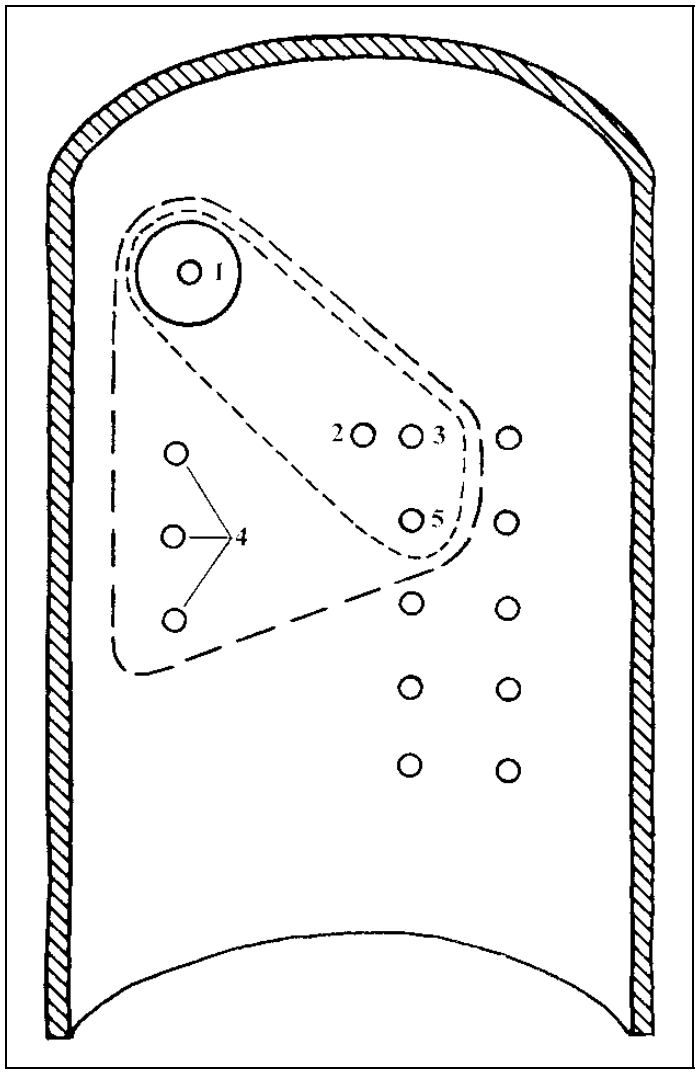

Figure 5 *The location of the surgically identified bronchial artery orifices in the descending aortic wall (aorta is opened through the area covered by pleura).* ***1)*** *Subcarinal artery.* ***2)*** *Variable artery, usually a right bronchial artery or a bronchial artery trunk.* ***3)*** *First right segmental artery.* ***4)*** *Left bronchial arteries.* ***5)*** *Second right segmental artery.* ***Outer ring:*** *The area in which bronchial arteries were found. Bronchial arteries to the left side were found anywhere in this area.* ***Intermediate ring:*** *The area within which a bronchial artery trunk and/or bronchial arteries to the right side were found.* ***Inner ring:*** *The area within which a subcarinal artery was found.*

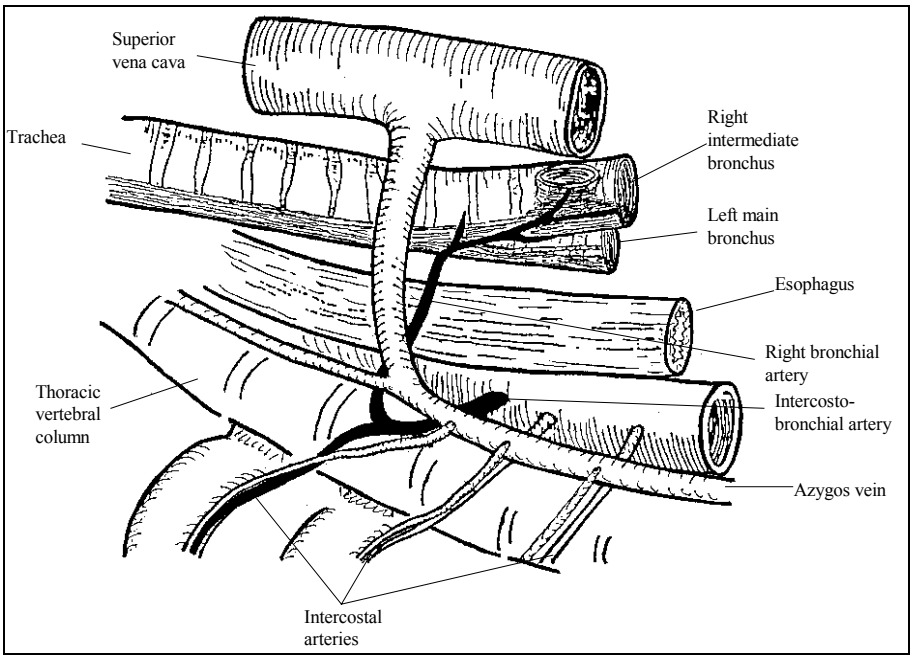

Figure 6 *Schematic drawing of the course of the right intercostobronchial artery (RICBA).*

Perfusion area of the bronchial arteries

By use of various study techniques, the bronchial arteries have been found to follow the bronchial tree deep into the lung parenchyma forming a peribronchial plexus, and small arterioles penetrate the muscularis to form a submucosal plexus [33]. The bronchial arteries also contribute arterial blood supply to the alveolar capillaries, the visceral pleura, the walls of the pulmonary arteries and veins as the vasa vasorum, the mediastinal tissue, the esophagus, mediastinal, hilar, and peribronchial lymph nodes, the pericardium, and the vagal and sympathetic nerves [19],[34]. In humans branches can be found even to the myocardium [35]. In these studies it has, however, not been possible to visualize the complete bronchial artery perfusion area, nor to quantitate the flow distribution between the various vascular segments.

Collaterals of the bronchial arteries

In addition to the bronchial arteries, originating from the proximal descending aorta, systemic blood supply to the lungs may originate from the subclavian, internal mammary, intercostal, subscapular, inferior diaphragmatic [36] and coronary [35] arteries. The collaterals from the coronary arteries are preserved in the heart-lung bloc, but in

isolated LTx all extrapulmonary collateral arteries are interrupted during harvesting of the donor lungs.

Venous drainage of the bronchial arteries

Studies of the microvascular anatomy have shown that the venous drainage goes to the azygos and hemiazygos veins [16], and through collaterals between the bronchial arteries and pulmonary alveolar microvessels, called "bronchopulmonary arteries" [34,37]. These collateral vessels measure 50-400μm and are coiled, possibly because of spiral musculature in their walls. It has been suggested that this structure might help to regulate the pressure gradient from bronchial to pulmonary vessels [37]. The intrapulmonary bronchial artery capillaries drain into the pulmonary veins [34,37], while the extrapulmonary bronchial artery capillaries drain to the azygos and hemiazygos veins [16]. In transplanted lungs the azygos/hemiazygos veins and the collaterals to the coronary circulation (except in HLTx) have been interrupted at transplantation. After transplantation all the bronchial artery blood flow drains into the pulmonary circulation. No study indicates that venous drainage is a problem after LTx with BAR, but such a problem remains a possibility.

Normal physiology of the bronchial arteries

Comparative anatomical studies of the bronchial arteries of different species conclude that the subgros anatomy of sheep, cow, pig, and horse is similar to the human anatomy [38]. Assuming also that the physiology of the bronchial arteries of animals is comparable with human physiology, animals have been used for establishing the basic knowledge about the physiology and pathophysiology of the bronchial arteries.

Measurement of the bronchial artery blood flow

Previous human bronchial artery blood flow measurements have been dominated/hampered by methodological difficulties often resulting in flow values that appear physiologically unrealistic.

A large variety of methods have been used to measure the bronchial artery blood flow in experimental animals. The simplest method used has been direct "cup-flow" [39]. Possibly more physiological flow measurements have been obtained by: Tracing microspheres labeled with color or radioactive isotopes [40-42], a variety of perivascular electromagnetic [43-46] and ultrasonic transit time flow probes [47-53], dye dilution techniques based on Fick's principle [54], a rotameter

(propeller) in the bronchial artery blood stream [55], or a pressure-controlled blood pump supplying flow to the bronchial artery trunk (as the only source) maintaining the same pressure in the bronchial artery trunk as in the aorta [56,57]. Most of these experimental methods measure flow with good precision. The bronchial artery flow of sheep has been studied by several authors, and unstimulated flow values corresponding to 0.4-1.1 % of cardiac output have been reported [43,45,51,54]. All the described methods used in animal experiments are based on the assumption that the bronchial artery blood flow derives from a common trunk that is easily accessible surgically. As previously described, this is unfortunately not the case in humans [13,15,16,18,20,32,II] .

Despite this a few studies of bronchial artery blood flow have been attempted in humans. Most of these studies have used dye dilution techniques and Fick's principle [58-61]. One such study estimated that the aorto-pulmonary collateral flow in 17 individuals without lung disease was up to 560 ml/min (8.2 % of cardiac output!) [58]. Another study (including nine healthy individuals) [62] found that bronchial artery flow was between -12 % and 23 % of cardiac output. In the same studies the bronchial artery blood flow in individuals with various lung diseases (tuberculosis, bronchiectasis, chronic obstructive pulmonary disease, cancer, silicosis, abscess, etc.) was -12 % to 55 % of cardiac output. The results indicate severe methodological problems.

In one study the bronchial artery flow was measured during extracorporal circulation as the return of blood to the left ventricle without forward main pulmonary artery flow in 40 individuals (with or without obstructive pulmonary disease) undergoing coronary artery by-pass surgery [63]. Under these conditions the flow was measured as 140±182 ml/min (SD) (3.2-4.2 % of the pump flow). In a similar study Deal and co-workers found that the bronchial artery flow was 3.8 ± 2.7 % of the pump flow [64]. Although measured under nonphysiological conditions (hemodilution, hypothermia, no ventilation, zero airway pressure, zero pulmonary artery pressure, zero left atrial pressure, and general anesthesia), these measurements per se appear more accurate and physiologically reasonable.

Regulation of bronchial artery blood flow

In animal studies bronchial artery blood flow is regulated by a number of physiological, pharmacological, and environmental stimuli.

Factors that decrease the bronchial artery blood flow are positive end expiratory pressure [40,55,65-67], increased left atrial pressure [56,66,68],

increased pulmonary artery pressure [68], bilateral vagotomy [55], and the anesthetic halothane [48].

Factors that increase the bronchial artery blood flow are hypercapnia [69], vagal nerve stimulation [66], adrenaline, serotonin or histamine [45,54-56,66], nitroglycerin, theophylline, acetylcholine [66], the β-agonist isoetharine [52], and high osmolality solutions such as hyperosmolar NaCl, dextrose, and x-ray contrast media (Omnipaque and Conray 66) [70].

The effects of hypoxia and pulmonary artery blood flow have been disputed. Baile and Pare found that hypoxia decreases the flow in dogs [69], while Wagner and Mitzner [71] (and Alsberge and co-workers [44] by hypoxic carotid body perfusion) found the opposite effect in sheep. Bloomer and co-workers found that pulmonary artery ligation increased the bronchial artery blood flow in dogs [72], while pulmonary artery clamping or embolization has the opposite effect in rabbits [40,42].

It has recently been hypothesized that endothelium NO production is an important pivot in the regulation of the bronchial artery blood flow: NO increased bronchial artery blood flow [49], while administration of the NO-synthase inhibitor N^{ω}-nitro-L-arginine-methyl-ester decreased the flow [49,52,53].

Lung transplantation with or without BAR

Arguments favoring BAR in LTx

Previous studies have indicated that the bronchial artery circulation could be beneficial to the lungs by the following effects:

- Improved airway healing and reduced risk of bronchomalacia.
- Improved lung infection defense including improved mucociliary clearance of the airways.
- Reduced edema formation after ischemia and re-perfusion.
- Less changes in airway cartilage morphology and reduced development of OB.

Airway anastomotic healing and bronchomalacia

BAR was re-investigated as a consequence of the poor airway healing observed after DLTx attempts with omental wrapping of the tracheal anastomosis [73]. Even if the patients survived there was still a high risk of bronchomalacia [74-76]. Although known to occur, the true incidence of bronchomalacia after SLTx without BAR in large transplant series has, to our knowledge, not been reported.

Lung infection defense

The role and response of the bronchial arteries during severe lung infection have been studied by Charan and co-workers in sheep with experimentally induced multiple lung abscesses [77]. The dense vascular plexus surrounding the walls of the abscess cavities was found to be exclusively supplied by bronchial arteries. In accordance with this finding Cudkowicz [78] found that the tuberculous cavities in five humans postmortem had a rich blood supply from bronchial arteries.

Mucociliary clearance

Normal/better resistance against infections could be an effect of preserved mucociliary clearance in lungs transplanted with BAR compared with transplants without BAR. In 1989 Paul and co-workers found that mucosal structures and function were altered in the early postoperative period after lung autotransplantation in dogs [79]. The investigators speculated that bronchial devascularization was the cause since these effects could be avoided by preserving (not dividing) the peribronchial tissue. In 1991 the same group reported that the mucociliary function was depressed early after lung autotransplantation in dogs, but that it recovered partially after 12 weeks [80]. The authors concluded that the recovery of mucociliary function should be attributed to spontaneous revascularization.

Post ischemic re-perfusion edema clearance

In an experimental study in sheep, Pearse and Wagner found less pulmonary vascular permeability and edema following re-perfusion after 30 minutes of pulmonary artery and bronchial artery clamping when both vascular systems were reperfused simultaneously than when only the pulmonary artery was reperfused [81].

Prevention of BOS and/or OB

BOS is defined by deterioration of lung function while OB is defined by appearance of histological changes in the airways (see definitions above). Although chronic rejection is considered the most probable cause of BOS/OB, several factors, including infection, rejection, and ischemia, may contribute to the development of BOS/OB [82].

Development of BOS and/or OB as a consequence of airway ischemia has been suggested by several authors [82-84].

Yousem and co-workers studied cartilage samples from the proximal bronchial tree of 30 lung or heart-lung transplanted patients who survived more than 45 days [83]. The transplantations were performed

without BAR but with omental wrapping of the airway anastomoses. The cartilage samples were obtained by autopsy (n=6) or open-lung or transbronchial biopsies (n=42). Ossification, calcification, and fibrovascular ingrowth into the normally avascular hyaline bronchial cartilage were observed in almost all the patients. The authors concluded that the observed changes indicated ischemia of the proximal airways, possibly contributing to the development of OB and bronchiectasis and an increased risk of infection.
The same group (Bando and co-workers [82]) studied 162 patients who survived more than 60 days (45 SLTx, 57 BLTx, and 60 HLTx). The evaluation of airway ischemia was based on bronchoscopy. Ischemic changes usually resolved within 14 to 21 days post transplant. Airway ischemia was identified by univariate analysis as a significant risk factor for the development of OB.

Arguments against BAR in LTx

- BAR introduces an extra source of postoperative bleeding.
- BAR prolongs the lung ischemic time.
- BAR failure could have serious adverse consequences.
- En bloc DLTx with BAR requires use of extracorporal circulation.

Intra- and postoperative bleeding

Some authors have argued that the mediastinal dissection necessary for performing the tracheal anastomosis for DLTx, as well as the retrocardiac dissection necessary for pulling the one lung behind the heart and great arteries, introduces a source of intra- and postoperative bleeding that is difficult to control because of poor exposure, while sequential bilateral lung transplantation requires less dissection and offers good exposure during the whole procedure [11,12,85].

Lung ischemic time

BAR will prolong the lung ischemic time corresponding to the extra time required for harvesting the bloc with preserved bronchial arteries, bronchial artery identification, and performing the BAR anastomoses (if BAR is performed before pulmonary re-perfusion). The reported extra ischemic time has varied between 20-22 minutes [25]and 30-40 minutes [14]. Performing BAR as the first anastomosis may reduce the lung ischemic time by 45-60 minutes [I], but bronchial artery re-perfusion may not be sufficient to prevent ischemic consequences.
Although DLTx may have a theoretical advantage over BLTx in reducing the ischemic time (for the second lung), it has been argued

that re-perfusion edema does not pose a clinical problem, and that no difference can be found in postoperative function between the first and last implanted lungs at BLTx. Indeed the second lung at BLTx is often free of the re-perfusion edema seen in the first implanted lung, which has been exposed to the entire cardiac output during implantation of the second lung [85].

Risk of cardiac complications at DLTx

In contrast to BLTx, extracorporal circulation is always needed in DLTx. It has been argued that extracorporal circulation introduces a risk of cardiac complications due to prolonged duration bypass, cardioplegia, and extensive manipulation of the heart [12]. Furthermore the dissection necessary for DLTx may denervate the heart [11].

Risk of bronchial dehiscence / necrosis if BAR fails

The department structure of most transplant centers has placed LTx with general thoracic surgeons, who do not usually perform coronary artery anastomoses, with vein or IMA grafts. Understandably, these general thoracic surgeons are reluctant to perform BAR.

Development of the surgical technique for BAR

At first sight the anatomy of the bronchial arteries presents a major argument against BAR. When it comes to organ harvesting, identification of the bronchial arteries, deciding on which bronchial artery orifices to revascularize and which not to, and performing BAR, the surgeon's anatomical knowledge and technical abilities are thoroughly tested. The IMA-bronchial artery anastomoses are of the same size as IMA-coronary artery anastomoses, or even smaller. By comparison with routine coronary artery surgery, an extra surgical difficulty is related to the quality of the aortic wall around the bronchial artery orifices.

We have tried to develop the surgical technique for BAR, to make it safe and reliable, as a basis for further scientific investigation of its effects on outcome after LTx.

Experimental animal studies, human cadaver studies, and early clinical experiences

A wide variety of experimental animals and operative methods have been used in the development of the operative technique for BAR.

As previously mentioned, Metras performed single lung transplantation with direct revascularization of the bronchial arteries in dogs already in 1950 [3]. Metras identified the donor bronchial artery in the descending aorta and reimplanted it with a cuff of aortic wall directly in the recipient descending aorta.

In 1964 Nettleblad and co-workers [86] reported successful BAR in canine left lower lobe transplantation after anastomosing a pouch of donor aorta, including the bronchial artery orifices, to the recipient's descending aorta in a side-to-side fashion.

In 1970 Mills and co-workers [87] studied the effect of BAR on outcome after left lung transplantation in 21 mongrel dogs (10 with, and 11 controls without BAR). The technique was identical to that used by Metras [3]. A 1 cm segment of the donor descending aortic wall, including the orifice of a left bronchial artery, was prepared and implanted in the recipient's descending aorta. Arteriography showed that BAR was patent in nine of the 10 dogs three weeks to three months post transplant. The dog with failed BAR died from dehiscence of the bronchial anastomosis seven days post transplant. The other nine dogs had normal bronchial healing, though one developed a minor bronchial ulcer. Nine of the 11 control dogs developed bronchial complications. Seven had ulcers, three had bronchial anastomosis dehiscence, and one developed a bronchial stenosis.

Nazari and co-workers [22] published a study in 1990 of left lung transplantation with BAR in 24 pigs. BAR was performed by anastomosing an aortic segment containing the bronchial artery orifice to the recipient's descending aorta. The operative mortality was high and the observation time was short, but postmortem injection of dye showed successful BAR in all 24 cases.

In 1990 Laks and co-workers [24] published a new method for BAR. The method was tested on five baboons; three had DLTx, one a left SLTx, and one a right SLTx. A pouch of the descending aorta (from proximal to the left subclavian artery to the level of the pulmonary hilum), including all the bronchial artery orifices, was prepared and anastomosed to the recipient's left subclavian artery or ascending aorta. In three surviving baboons (one DLTx, two SLTx) angiograms after 14 days and postmortem examinations after 22, 30, and 30 days

demonstrated patent anastomoses, no pouch thrombi, and normal healing of the tracheal or bronchial anastomoses.

Human studies

In 1990 Schreinemakers and co-workers [20] published an anatomical study of the bronchial arteries in 30 autopsy cases. Based on these studies, a technique for harvesting the lungs including preservation of RICBA, was developed. In 17 of 19 dissections it was possible to prepare a bronchial artery pedicle with a segment of aorta containing the origin of the RICBA. It would have been possible to re-implant the aortic cuff holding the RICBA orifice into in the ascending aorta of a recipient after DLTx.

Preceding the clinical introduction of BAR, Dubrez and co-workers dissected the tracheobronchial blood supply in 20 human cadavers, and performed angiographic studies in 50 patients [13].

Clinical experiences

In 1973 Haglin and co-workers [4] reported the first clinical LTx case in which direct BAR of the left lung had been performed using a method very similar to that earlier described by Metras [3] and Mills and co-workers [87].

Couraud and co-workers [14] introduced the use of a vein graft conduit and were the first to publish a small regular series of patients who had undergone DLTx with BAR. The organ harvesting was done according to the method described by Schreinemakers and co-workers [20]. The DLTx method included a tracheal anastomosis, and BAR was done using a saphenous vein graft conduit from the recipient's ascending aorta primarily to the origin of the RICBA, though in a few cases one or more left bronchial arteries in the donor descending aorta were also included. The conduit-to-bronchial artery anastomosis was performed on a side-table before introducing the donor lungs into the recipient. The proximal vein conduit-to-aorta anastomosis was done as the last anastomosis at the end of the operation. Couraud and co-workers [14] stressed that, in order not to interfere with the bronchial blood supply, dissection around the carina and individual mobilization of the bronchial arteries should be avoided. The additional ischemic time needed for performing BAR was estimated at one hour. The bronchial blood supply was evaluated by repeated endoscopic examinations of the airway healing, and in seven patients by arteriography two weeks postoperatively. The arteriography showed an open vein graft with visualization of bronchial arteries in five patients, while two showed

thrombotic occlusion of the vein graft. Normal tracheal healing was observed in all the patients. Later, in 1991, Couraud and co-workers [88] had enlarged the primary material by three additional patients, two of whom had received DLTx and one a right SLTx. No patient had anastomosis healing problems or stenosis. Arteriography was performed in two of the additional patients and showed a functional saphenous vein graft and visualization of the bronchial arteries.

In 1993 Daly and co-workers [25] published a series of eight patients from Harefield Hospital, London, who had undergone nine DLTx with BAR. Their organ harvesting method was similar to that described by Schreinemakers and co-workers [20]. The bronchial arteries were identified and confirmed by probing. The largest vessel going in the direction of the carina was chosen for revascularization with the left IMA. The IMA graft was chosen instead of a saphenous vein graft because of expected better long-term patency. The IMA-to-bronchial artery anastomosis was performed as the last anastomosis. The orifice of the bronchial artery was brought into view by pulling on the cephalic end of the donor aorta. Back-bleeding confirmed the identity of the bronchial arteries. Orifices in the donor descending aorta that were not revascularized but produced backbleeding were oversewn. The additional time needed to perform BAR was estimated at 30-60 minutes, and the additional donor organ ischemic time was estimated at 20-22 minutes. The bronchial blood supply was evaluated by repeated bronchoscopies and an arteriography performed 12 days to two months postoperatively. In all the patients but one the IMA grafts were patent with good bronchial artery perfusion and normal healing of the tracheal anastomoses. The patient with arteriographic bronchial artery occlusion developed a large ulcer at the tracheal anastomosis.

In 1994 Daly and McGregor [28] published the results of BAR in 10 SLTx from the Mayo Clinic, Rochester, Minnesota, USA. The additional ischemic time used for the revascularization procedure was estimated at 15-20 minutes. In nine surviving patients angiography demonstrated excellent perfusion of the bronchial arteries in seven and no perfusion in two. Bronchial healing was normal in all the patients. Daly and co-workers were the first to demonstrate that it was possible to perform bronchial revascularization of two single lungs from the same donor by dividing the donor aorta and the mediastinal tissue between two bronchial arteries.

When LTx was started in Copenhagen in 1992 it was decided that BAR should be performed whenever possible, and that the first choice procedures should be DLTx with BAR or SLTx with BAR. In 1994 the

results were published of the first 14 DLTx with BAR from Copenhagen, using a left IMA conduit [26]. The material has later been expanded to 66 DLTx, one BLTx (with BAR of the right lung), 26 SLTx, and nine HLTx. The surgical results have been presented in several publications [89-92**I**,**II**,**IV**].

Current Copenhagen BAR technique

Organ harvesting and preservation

In principle the donor operations have been performed as previously described by Schreinemakers and co-workers in 1990 [20], Couraud and co-workers in 1992 [88], and Daly and co-workers in 1993 [25]. The lungs were preserved with modified Euro-Collins solution. The heart and lungs were removed en bloc with the trachea, esophagus, and descending aorta in order to preserve the retroesophageal RICBA. The organs were stored in ice-cold Ringer's solution during transport.

Bronchial artery identification

After opening the donor descending aorta corresponding to the pleura covered part, bronchial artery identification was done by inspection, palpation, and probing **[I]**.

Dividing the bloc for SLTx

When dividing the lung bloc for SLTx, anatomical realities often result in less than ideal conditions for revascularization of more than one lung. Overambition may result in unsuccessful or failed BAR for both lungs. Our surgical technique for SLTx has changed slightly with time, because we realized that a larger percentage of BAR attempts failed in SLTx (unpublished information) than in DLTx.

Choice of conduit for BAR

When BAR was introduced in Copenhagen there was knowledge of the work of Couraud and co-workers using a saphenous vein conduit [14], and of the work at Harefield Hospital using an IMA conduit [25]. Based on the expected better long-term patency, the IMA conduit was chosen. Using this conduit in the first 50 DLTx, nine HLTx, and six SLTx, we were able to perform BAR to 90 % of the identified bronchial arteries. The extra operative time used for this procedure was estimated at 30 to 45 minutes in DLTx **[I]**.

Performing the BAR anastomosis(-es)

The method we used at implantation was a modification/development of the method developed by Daly and co-workers [25]. The technique has since been further modified and simplified by changing from performing BAR as the last anastomosis to performing it as the first anastomosis. To perform BAR, the lung bloc is first introduced into the left pleural cavity and the right lung is gently pushed through the pericardial openings and mediastinum behind the heart to the right pleura. The left lung is lifted up and hung backwards over the heart, exposing the bronchial artery orifices in the donor descending aorta on top of the heart, and thus optimizing the conditions for performing the anastomoses. Single or sequential anastomosis/-es are performed to the selected bronchial artery orifices using 7-0 monofilament sutures. Following removal of the IMA bulldog clamp, successful BAR is immediately confirmed by bleeding from the donor mediastinal tissue. We have observed no indications that the early re-perfusion is either harmful or beneficial to the lungs.

When the lung bloc is divided for two SLTx, we now give priority to the lung with the most favorable anatomy for performing BAR. The patient is given 5000-10000 IU of heparin before the pulmonary artery re-perfusion to prevent clotting of the bronchial circulation while performing the BAR anastomosis. BAR in SLTx is performed as the last anastomosis, adding no extra organ ischemic time.

Extracorporal circulation and myocardial protection

DLTx requires use of extracorporal circulation. We have used bicaval venous cannulation, high aortic cannulation, and left ventricular venting. The patients were cooled to 25^{o}-28^{o}C. The heart was kept continuously fibrillating by fast rate pacing. Myocardial function after hours of fibrillation has been uniformly good, and we have experienced none of the cardiac problems described after DLTx by The Toronto Lung Transplant Group [73]. Difficult weaning from cardiopulmonary by-pass in one case was caused by coronary artery disease and thrombosis. High dose aprotinin has been part of the protocol [93].

For SLTx, the need for extracorporal circulation does not relate to BAR or no BAR.

Surgical and anatomical results of BAR

Surgical identification of the bronchial arteries

With increased experience the number of bronchial artery orifices identified per donor increased throughout the series, from 1.6 bronchial arteries per donor at the start of the series to 2.9 at the end [II] (**Figure 7**) (we expect no further increase). While the location of the right bronchial arteries was quite constant, usually located as the first (and largest) right segmental artery, the location of the left bronchial arteries was more variable [II]. In our published surgical series [II], we never identified more than four bronchial artery orifices per donor lung bloc, though later we identified five bronchial artery orifices in one bloc (out of total of 94 blocs).

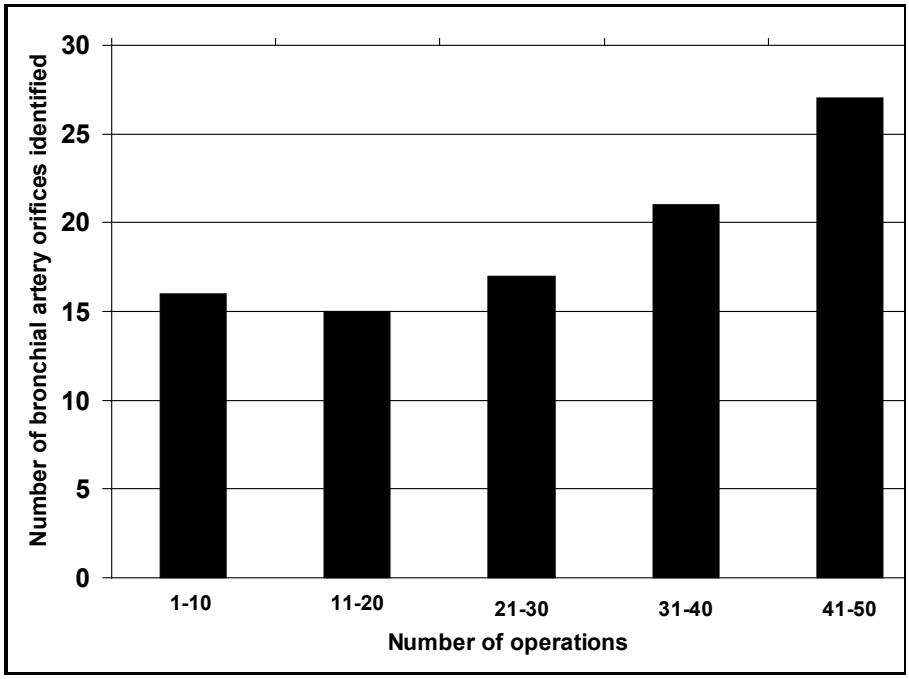

Figure 7 *The learning curve for identification of bronchial artery orifices in the donor aorta. The number increased from identification of 16 orifices during the first 10 operations to 27 orifices during operations 41-50. The number of identified orifices is not expected to increase further.*

The accuracy of the surgical identification of bronchial arteries is limited by minimal dissection and handling of the bronchial artery orifices, and no use of contrast medium. Sometimes possible bronchial artery orifices are excluded from further surgical assessment due to

small size and/or unfavorable location. When one or more identified bronchial artery orifices are difficult to revascularize, it is good to know that the chance of collateral filling of those arteries is still good [II].

Perforation of a bronchial artery during probing occurred once but fortunately the artery could be repaired and successful BAR was performed.

Nomenclature of the bronchial arteries

Based on the arteriographic findings, we have developed a nomenclature for the bronchial artery system. The nomenclature was developed with the aim of easy description of the surgical results; and the names are based on the anatomical locations of the arteries, which can be named regardless of the central anatomical pattern present [II].

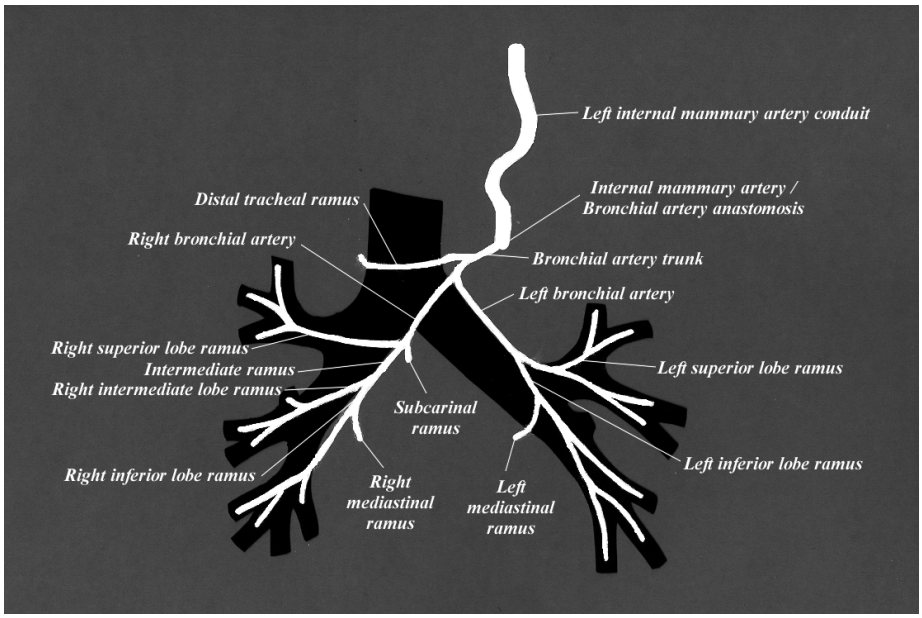

Figure 8 *The bronchial artery tree with our suggested nomenclature.*

Classification of the surgical BAR result by arteriography

Routine internal mammary - bronchial arteriography was performed approximately one month post transplant to evaluate the surgical result, and to classify the it for use in further studies. The mammary-bronchial arteriography was performed using the Seldinger technique and cinematographic recordings during selective contrast medium injection into the IMA conduit. All the cine films were studied together with the surgical records, and schematic drawings of the vascular anatomy were

made in each case. The arteriographic results were classified according to the following classification system, which applies to SLTx, DLTx, and HLTx with BAR):

Complete BAR: Clear visualization of bronchial arteries on the transplanted side or sides (DLTx, HLTx, SLTx). Each lobe is supplied by a least one lobar ramus. **(Figure 9)**

Incomplete bilateral BAR: Visualization of bronchial arteries on two transplanted sides but one or more lobar rami were missing (DLTx, HLTx) **(Figure 10)**.

Incomplete hemilateral BAR: Clear visualization of bronchial arteries on only one transplanted side (out of two)(DLTx, HLTx) **(Figure 11)**.

Incomplete poor BAR: Sparse visualization of bronchial arteries on any transplanted side (SLTx, DLTx, HLTx) **(Figure 12)**.

Failed BAR: No visualization of bronchial arteries **(Figure 13)**.

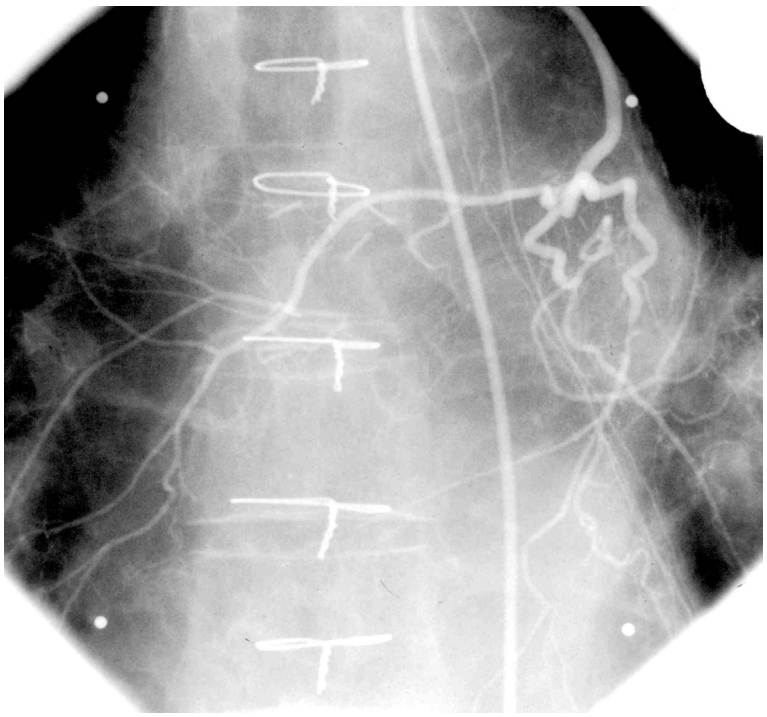

Figure 9 *Complete BAR.*

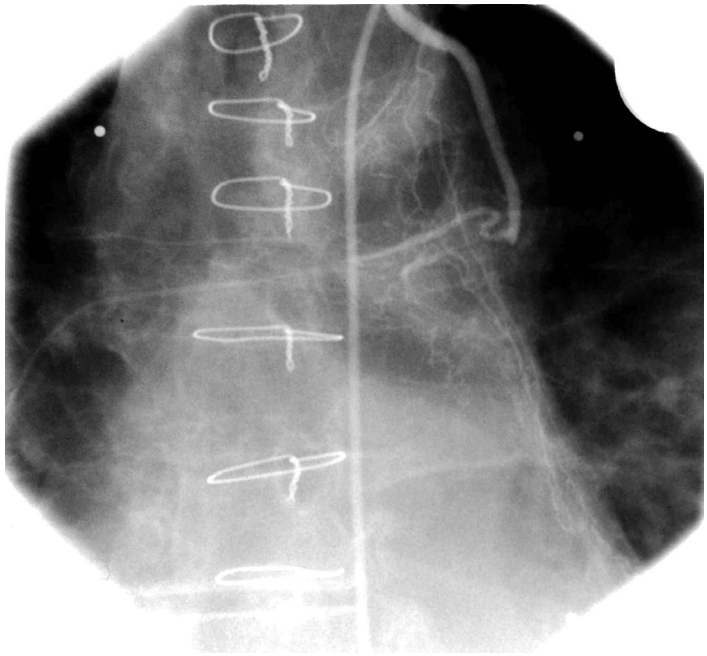

Figure 10 *Incomplete bilateral BAR.*

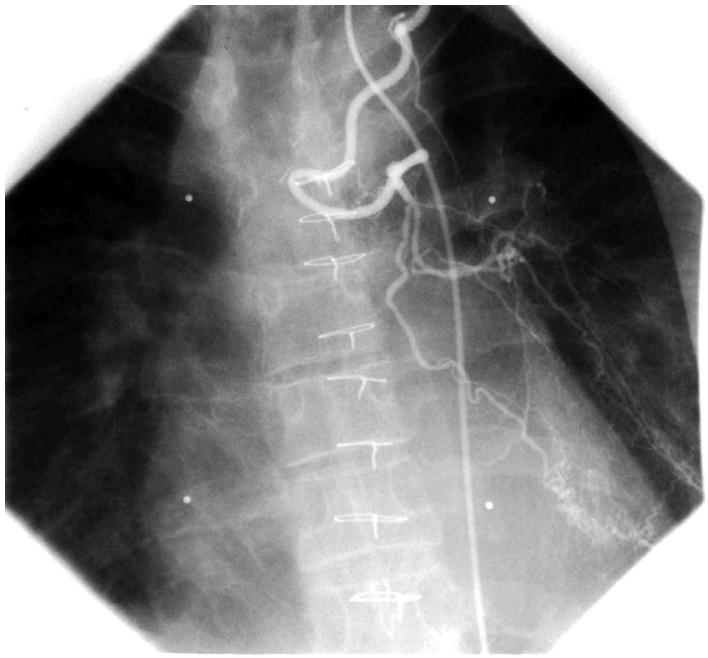

Figure 11 *Incomplete hemilateral BAR.*

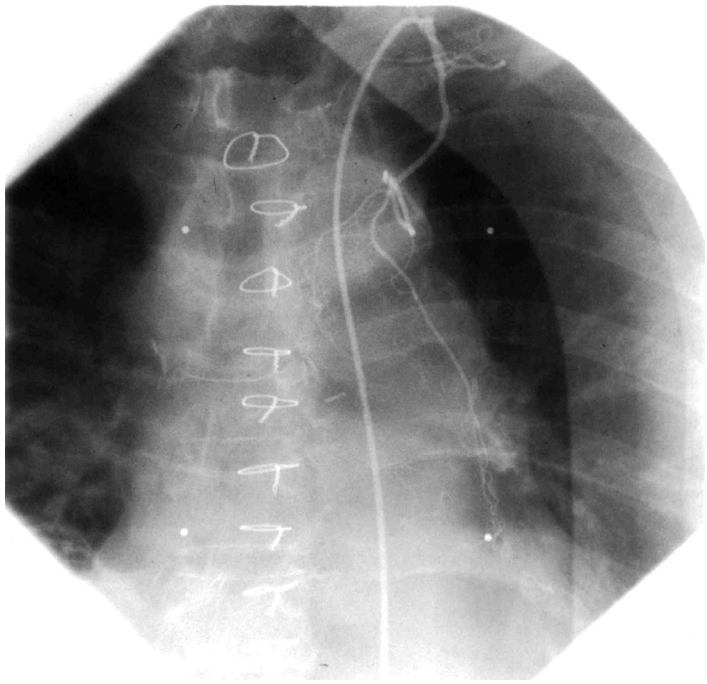

Figure 12 *Poor BAR.*

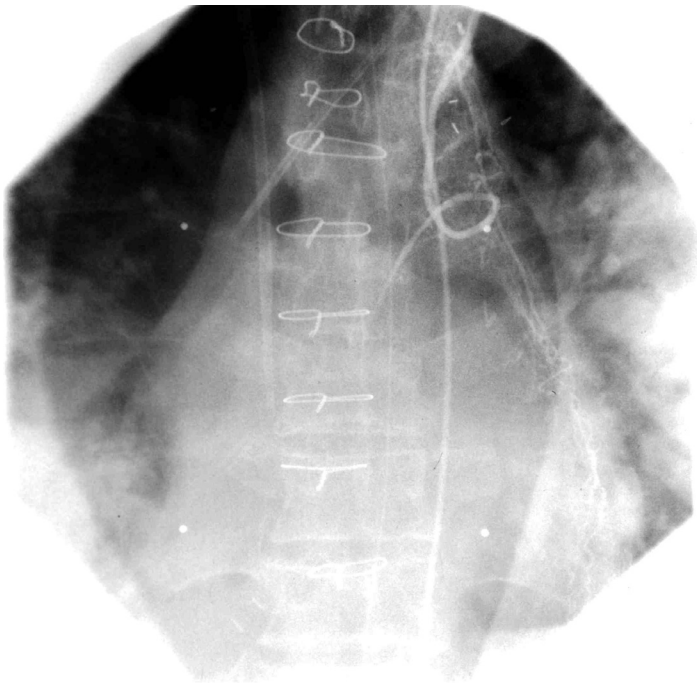

Figure 13 *Failed BAR.*

Arteriographic results

Our initial arteriographic study included 43 DLTx, six HLTx, and four SLTx. Arteriographically visible bronchial artery blood supply to all transplanted lung lobes (complete BAR) was found in 58 % after DLTx, 50 % after HLTx, and 100 % after SLTx [II]. In 18 patients (15 DLTx and three HLTx) BAR was classified as incomplete, and in three DLTx patients BAR was classified as failed.

Arteriographic versus surgical identification of bronchial arteries

Analysis of our arteriographic data showed a discrepancy between the number of surgically identified bronchial artery orifices and the number of bronchial arteries visualized by arteriography. The surgeon was good at identifying the RICBA, while in most cases an arteriographic bronchial artery trunk was incorrectly identified as a left bronchial artery or a subcarinal artery. In the 43 DLTx and six HLTx patients who underwent arteriography, the number of surgically identified and revascularized right bronchial arteries was 52, while 55 were visualized at arteriography. The corresponding numbers for the left bronchial arteries were 40 and 73. The difference is mainly explained by the fact that only five bronchial artery trunks were recognized surgically, while 32 trunks were visualized at arteriography. Dilatation of small, non-identified collaterals may also contribute to explaining this difference. The incomplete identification of the anatomy reflects the limitations of the surgical method used at transplantation. The surgeon's primary goal was to identify the bronchial artery orifices that were possible to revascularize; swiftly and without traumatizing the tissue. To improve the peroperative identification of the bronchial artery anatomy, we have considered cannulating possible bronchial artery orifices with a buttoned cannula and injecting a colored medium or heparinized blood, but we have refrained from this in order not to damage the orifices or the endothelium of the arteries. Given these limitations, we still find good accord between our peroperative identification of bronchial arteries and the normal anatomy as established in cadaver studies by others.

Central anatomical patterns of the bronchial arteries

Centrally in the mediastinum we found various bronchial artery branching patterns (**Figure 14**), and their frequencies were compared to the findings of Uflacker and co-workers [94]. The commonest pattern in their and our studies was one right and one left main bronchial artery,

contrasting to the findings of Cauldwell and co-workers [15], Liebow [16], and Kasai and Chiba [18]. However, there are two limitations in our study: First, our series included a learning process for identifying the bronchial artery orifices. Second, although we only included patients with arteriographically "complete BAR" in our description of the central anatomical patterns, the term "complete BAR" only means that each transplanted lung lobe received at least one bronchial artery ramus. While Uflacker, Cauldwell, Liebow, Kasai, and co-workers attempted to visualize all the available arteries, we know that we were not always able to revascularize all the arteries. Bronchial arteries overlooked during surgery will therefore result in incorrect distribution between different central anatomical patterns. The findings of Uflacker and others were probably more correct.

We found that the donor side of the tracheal anastomosis could be supplied from four different vessels: direct from the aorta (a subcarinal artery), from a right or left bronchial artery, and/or from the right superior lobar ramus of the right bronchial artery [II].

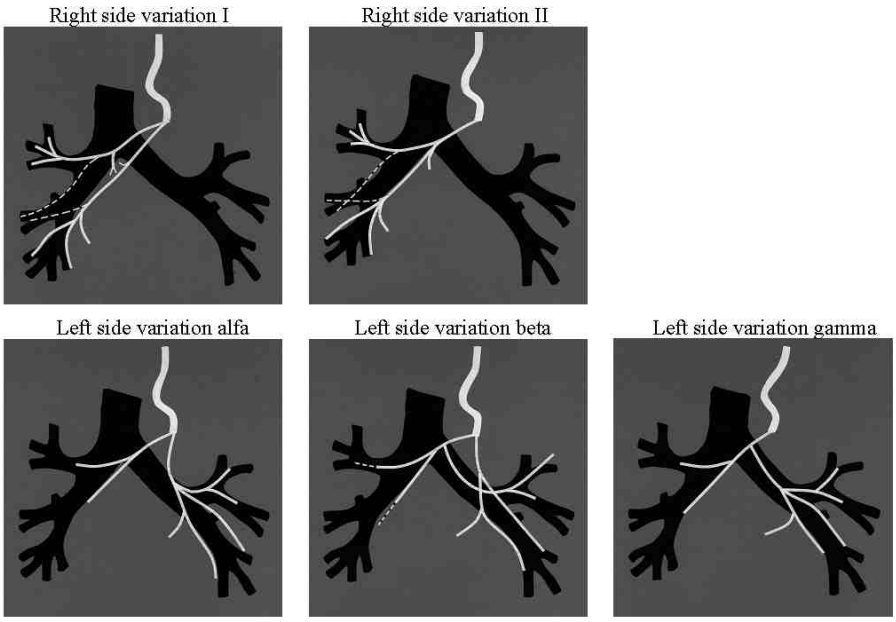

Figure 14 *Central artery anatomy patterns (the bold curved line illustrates the mammary artery. The thin lines illustrate the bronchial arteries).*

Patency of BAR

If BAR is to influence the long-term results after LTx, long-term patency should be important. The two year patency of BAR was investigated in 20 DLTx, one SLTx, and two HLTx patients who survived two years or more [III]. The appearance of the bronchial arteries was unchanged after two years in 11 patients. Increased vascularity was found unilaterally in two patients, and bilaterally in seven patients. New vessels, not visible on the first arteriography, had appeared in three patients. Four arteriographies, primarily classified as incomplete bilateral BAR, had improved to fulfill the criteria for reclassification as complete BAR. In four patients, one or more small vessels visible on the first arteriography were not present on the second. We found no arteriographic evidence of bronchial artery disease, i.e. vascular disease of the bronchial arteries comparable with the coronary artery disease observed after heart transplantation. Nor did we find any evidence of arteriosclerotic disease in the mammary artery.

Sensitivity and safety of bronchial arteriography

Arteries down to diameters of approximately 0.4 mm could be visualized with the present IMA-bronchial arteriography technique [V]. This was sufficient for visualizing the bronchial artery arborization well beyond the lobar ramus level.

We had one complication out of 150 IMA-bronchial arteriographies performed 1992 - 1998. At an arteriography performed one month after SLTx the IMA was open and BAR was classified as complete. However, the IMA closed during the course of the examination. Local injection of Actilysis® directly into the IMA was without effect after 20 minutes. At the two-year re-arteriography, the IMA had re-opened and BAR was again classified as complete. No clinical side effects were observed.

Bronchial artery perfusion scintigraphy

In lungs transplanted with BAR only one feeding artery for the bronchial artery system is present. This offers a unique opportunity to visualize and quantitate the distribution of the bronchial artery blood flow. A scintigraphic method was applied in 22 DLTx patients [V]. At the end of the arteriographic examination ^{99m}Tc-labeled macroaggregated albumin particles were slowly injected directly through the arteriographic catheter, into the IMA and the bronchial circulation. The particles were trapped at the pre-capillary level. The distribution of radioactive activity was then recorded and visualized by

gamma camera imaging. The typical finding was an "H-shape" distribution of the radioactivity, with the center of the "H" located around the carinal area and near the pericardium. The arms of the "H" were located in the upper and lower lung lobes (**Figure 15**). Radioactivity in the central as well as in the peripheral parts of the lungs was definitely higher than the background activity in all patients studied. We assume that the "H" shape activity reflects blood flow to the main bronchi and associated peribronchial tissue, including lymph nodes.

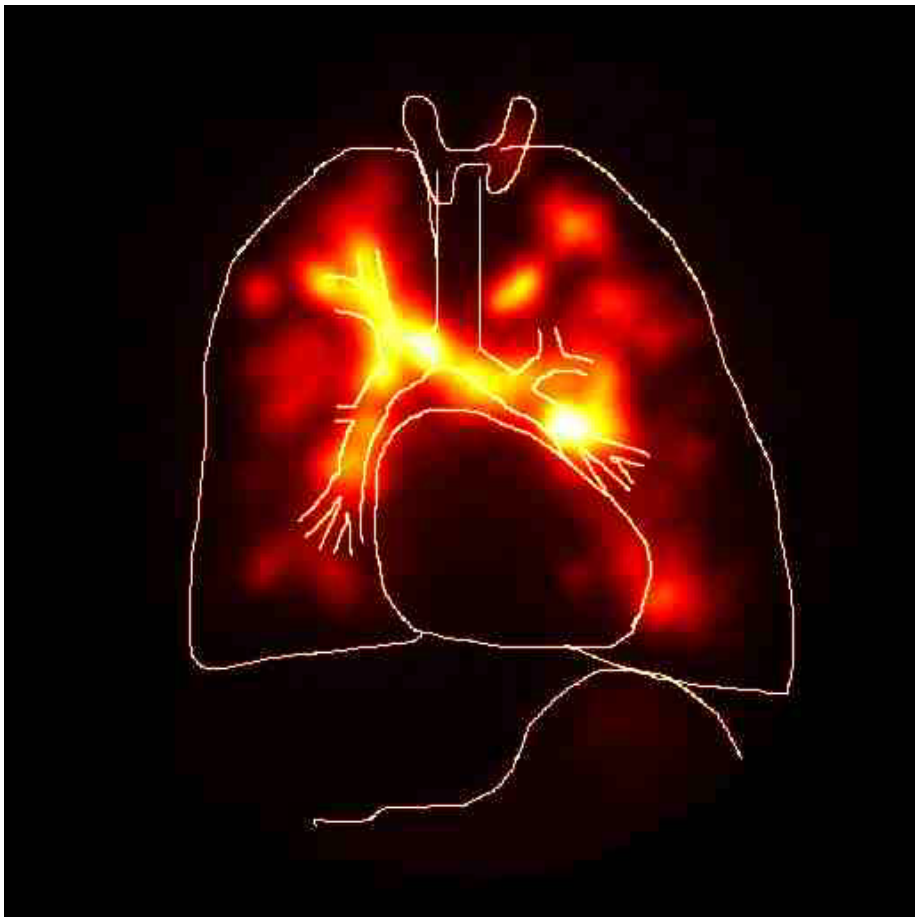

Figure 15 *Bronchial artery scintigraphy with superimposed schematic outline of major thoracic structures.*

Another distinctive finding in most scintigrams was a patchy "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. Finally, the study demonstrated that, even though the major part of the flow supplied central structures, some flow reached the most peripheral parts of the lungs. The tracer could reach the peripheral areas directly through bronchial arteries, or indirectly due to shunting through the "bronchopulmonary arteries" into the pulmonary arterial network.
We found no visual or quantitative differences between scintigrams from patients studied one month after DLTx (n=13) and patients studied two years after DLTx (n=9). This confirmed our arteriographic study of the medium term patency of BAR, from which we concluded that the bronchial vascularity two years post transplant remained unchanged or even improved, compared with one month post transplant [III].

Physiological effects of BAR

Direct measurement of bronchial artery flow

For BAR to be of clinical importance blood flow through the bronchial arteries should be not only present, but also sufficiently large. On the other hand, too large a bronchial artery blood flow, larger than physiologically or metabolically required, would be a systemic artery to pulmonary vein shunt.
As described above previous attempts to measure normal human bronchial artery blood flow have been complicated by methodological problems. Therefore we do not know the normal bronchial artery blood flow "target level".
Sundset and co-workers demonstrated that the blood flow of the airways of transplanted lungs is influenced by BAR [95]. Using laser Doppler flowmetry, the authors demonstrated that, in five out of seven DLTx patients with BAR, clamping of the IMA-conduit reduced the airway epithelium perfusion by 10-60%. The results indicated that the airway perfusion of transplanted lungs was higher, but also more heterogeneous, than the airway perfusion in a control group of patients undergoing coronary artery by-pass grafting. This finding was in accordance with previous experimental findings by Aoki and co-workers [96]. These authors performed experimental left lung transplantation in dogs, with and without BAR. BAR resulted in significant improvement of graft bronchial blood flow compared with transplantation without BAR. However, restoration of bronchial perfusion to normal levels could not be achieved, suggesting an irreversible defect in the microcirculation of the donor airways.
We performed direct measurements of the bronchial artery blood flow in eight DLTx patients with arteriographically confirmed complete BAR. With the entire bronchial artery blood flow coming from the

IMA-conduit, direct measurement of the blood flow velocity could be performed using a 0.014" Doppler guidewire, placed in the lumen of the IMA. After establishing the IMA diameter by arteriography, the flow through the IMA into the bronchial arteries could be calculated. The inaccuracy of these flow measurements was related to two factors: the measurement of the IMA diameter and of the flow velocity. In the eight DLTx patients included in this study, basal bronchial artery flow values from 19-67 ml/min were measured. In three patients nitroglycerin and verapamil injected directly into the IMA increased the bronchial artery flow to 121 - 262 % of basal values (31 - 89 ml/min), indicating that the bronchial artery vascular bed is pharmacologically responsive, also after transplantation. The flow values recorded in this study appear more physiological than previous bronchial artery blood flow values obtained in humans. The bronchial artery blood flow values we have measured were, however, snap-shots of the flow under the given circumstances, and there are many reasons to dispute whether these flow values, measured in transplanted lungs, are comparable to the bronchial artery flow in healthy individuals [VII].
The high bronchial artery flow values found in two out of three patients with severely reduced lung function in this study suggest that these parameters are correlated, though not statistically significant in this small material. The high flow could be caused by an ongoing process (infection or rejection) in the lungs. It would be valuable further to study bronchial artery flow changes in response to rejection, infection, and other lung insults.

Lung infection, airway clearance, and ciliary beat frequency

A presumed benefit of BAR is reduced frequency and severity of infections in the transplanted lungs by improved mucosal function and resistance, including preserved mucociliary clearance in the trachea and bronchial tree.

Lung infection

The influence of BAR on the incidence and severity of episodes of pulmonary infection is difficult to study, since diagnostic criteria for such episodes are not precise. Continuous prophylactic antibiotic treatment and temporary over-medication, reflecting an aggressive clinical approach when infection is suspected, blur the picture further.
We have chosen to define an episode of pulmonary infection episode as a minimum period of three days of antibiotic or antiviral medication. The three day limit was chosen to avoid including shorter episodes of

antibiotic treatment as episodes of infection, before the diagnosis of rejection was established [IV]. For patients developing BOS and/or OB or not the mean number of infection episodes per observation year was 2.3 ± 3.1 (SD) and 2.1 ± 3.7 (SD), respectively (not significant). For the 62 DLTx patients included in this study, the mean number of infection episodes per observation year was 2.1 ± 3.5 (SD). None of these patients developed a lung abscess. As the microbiological, sociological, cultural, and climatic conditions are most variable between transplant centers, a direct comparison of our infection rate with the infection rates from centers not performing BAR has not been attempted.

Ciliary beat frequency

The ciliary beat frequency (CBF) has been used in previous studies as an indicator of mucociliary clearance [97].

Two groups have previously investigated CBF in lung transplant recipients, with contradictory results [98,99,99]. One group, which studied five patients, found that there was no significant difference between the CBF proximal and distal to the airway anastomosis, and that the transplanted bronchus CBF was not different from that of untransplanted controls [98]. However, another group, which studied six patients, found that the CBF of the transplanted lung bronchus was significantly lower than that of the contralateral (native lung) bronchus [99].

We investigated whether the re-establishment of normal bronchial artery flow by BAR in transplanted lungs would contribute to preserved or even improved mucociliary clearance. We studied this indirectly by measuring the CBF of epithelium cells in bronchial mucosa samples, and by histological examination of the epithelium samples, including quantification of the number of columnar epithelium cells versus metaplastic/squamous epithelium cells, and of ciliated columnar epithelium cells versus deciliated cells [VI]. We found that the CBF of transplanted lungs did not differ from that of native lungs and consequently BAR did not have any demonstrable influence on the CBF. However, one factor that may have influenced the result was that the biopsies were taken after the patients had been ventilated with 100% oxygen for at least 10 minutes. This may have “resuscitated” mucosal cells that were otherwise ischemic. Histological findings indicated that the presence of ciliated cells, or the presence of cilia on columnar epithelium cells, was normal or close to normal even without BAR. A small number of metaplastic cells were found in airways

without successful BAR, but never in airways with successful BAR. It is possible that successful BAR prevents epithelial metaplasia. The only additional "positive" finding was that presence of excessive secretion in the airways was significantly associated with increased CBF.
Before finally closing the issue of epithelium function and mucociliary clearance after LTx, there may be need for another direct study of mucociliary clearance (ideally including simultaneous CBF measurements) in a larger number of patients.

Post ischemic re-perfusion edema
In DLTx the operation was modified so that the IMA to bronchial artery anastomoses were performed as the first anastomoses, and the IMA conduit was left open during the rest of the procedure, allowing continuous bronchial artery perfusion. Although preservation of the bronchial artery circulation may reduce post ischemic re-perfusion edema, as indicated by the experiments by Pearse and Wagner [81], we were worried about early re-warming of the lungs and possible warm ischemia. Fortunately, we have so far not been able to detect any such harmful effects, and re-perfusion edema, judged by the postoperative chest X-rays and the clinical course, has been rare in lungs transplanted with BAR. No quantitative or comparative study of postoperative pulmonary edema or lung water has been performed.

Clinical outcome after LTx with BAR

Perioperative bleeding
One major concern when performing BAR is bleeding from the posterior mediastinal tissue and the lung hila, which are not easily accessible. In our initial series, including 47 DLTx cases, bleeding was a clinical problem intraoperatively in two patients, and postoperatively in five patients [I]. Intraoperative bleeding from the IMA-bronchial artery anastomosis was stopped by additional hemostatic sutures in one patient, resulting in failed BAR recognized by an arteriography immediately postoperatively. The patient was re-operated and bronchial artery flow re-established (complete BAR at re-arteriography). In another patient intraoperative bleeding was located to a bronchial artery lesion. The lesion was repaired and arteriography showed complete BAR.
During the first 24 hours, postoperative bleeding varied between 0.8 and 4.2 liters. Five patients underwent re-operation because of bleeding. In three of these the IMA-bronchial artery anastomosis was a

major source of the bleeding, one was bleeding from a steel wire perforation of the right IMA, and one was without any single major source of bleeding. All the IMA-bronchial artery anastomotic bleedings were in the first half of the series when 2-3 bronchial artery orifices were often covered with a single IMA anastomosis. This technique was later changed in favor of performing sequential anastomoses whenever the distance between the bronchial artery orifices exceeded 5-6 mm.

Airway healing

In our initial arteriographic study, including 50 DLTx, nine HLTx, and six SLTx, bronchial healing was normal in all but six patients, of whom five had an arteriography performed.

All three DLTx patients with arteriographically failed BAR developed tracheal bronchial ischemia impaired bronchial healing. In two of these patients, early mucosal necrosis below the tracheal anastomosis and in the main bronchi was followed by stenosis of the left main bronchus. Both patients finally had to be treated with left-sided pneumonectomy, but they survived with their remaining right lungs. The third patient was a re-transplantation after single left lung transplantation. Before the transplant the patient was chronically infected with pseudomonas and aspergillus, and after DLTx early development of infectious membranes prevented thorough bronchoscopic examination of bronchial mucosal vascularization. The patient died from the pulmonary sepsis 30 days after the operation.

Obliterative bronchiolitis and bronchiolitis obliterans syndrome

Irreversible loss of lung function within a few years remains a frequent problem and cause of death after LTx. These patients have BOS as defined by the ISHLT formulation [1], and many of them have histological evidence of OB [2]. Although most patients with BOS have OB, and vice versa, this is not always the case.

Baudet and co-workers [92] studied 15 patients with attempted BAR and a follow-up of 22 to 69 months. Of five patients with failed / closed BAR, all had clinical BOS (four had histological OB), while none of seven patients with functioning BAR had BOS or OB. The authors concluded that patent BAR might protect against the development of BOS and OB.

We studied 62 DLTx patients, of whom 53 had a survived more than six months (mean follow-up 31 months, range: 6 - 61 months) and were as such at risk of developing BOS. Fifteen of the patients had developed BOS. The mean onset time ($\pm$SD)of BOS was 18 $\pm$ 11 months

postoperatively. OB was diagnosed in seven patients 31 ± 15 months post transplant, 17 ± 16 months after the BOS diagnosis. Nine of the BOS patients showed no histological signs of OB, while in the other six BOS preceded OB. One patient has developed OB 25 months post transplant without yet developing BOS.

For the 42 patients who survived three months or more post transplant and who did not develop BOS, the mean (±SEM) postoperative baseline FEV_1 was 94.0 ± 3.3 percent of the expected normal FEV_1. This was significantly better than the postoperative baseline FEV_1 of patients who later developed BOS (p=0.007 by Mann-Whitney U-test). In this group (n=15) the postoperative baseline FEV_1 was only 76.6 ± 6.1 percent (SEM) of the expected normal FEV_1.

For patients who developed BOS and/or OB, the onset time was not significantly different for patients with arteriographically complete or incomplete bilateral BAR compared with patients with incomplete hemilateral, incomplete poor, or failed BAR. However, the numbers are small, and failed BAR has been associated with severe airway complications and/or death. Nor did we find any correlation between the number of episodes of pulmonary infection or rejection and the development of BOS and/or OB.

Since we did not have any comparable group of lung transplanted patients without BAR in our center, we compared our results with results after BLTx published and obtained through personal communication from another transplant center, Stanford University. Using the same selection criteria as previously used by Stanford University (n=26) on our patients (n=38) with complete or incomplete BAR, our actuarial curve of patients free from OB and/or BOS seems to be better than the corresponding results from Stanford University (**Figure 16**). However we were not able to apply any statistical analysis for these curves, since all the raw data from Stanford University was not available. If the difference was a true finding it may, in addition to being a consequence of BAR, be partly explained by slightly different time periods. Other possible explanations for the apparent difference in freedom from BOS and OB could be based on geographic, ethnic and microbiological differences between the institutions. However, it is quite striking that the development of BOS and/or OB seems to be delayed fortwoyears or more in DLTx patients from Copenhagen with complete or incomplete bilateral BAR compared with BLTx patients from Stanford University.

Although Baudet and co-workers [84] and we [**IV**] have found a possible beneficial effect of BAR on the development of BOS, the number of

patients was small and follow up short. To confirm these results, further studies of larger numbers of patients are required.

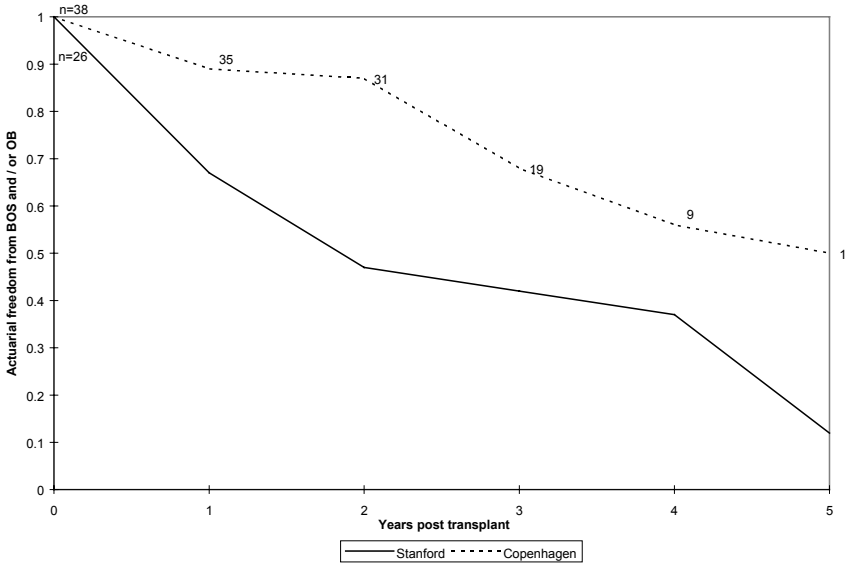

Figure 16 *Actuarial freedom from BOS and/or OB 0-5 years for patients surviving > 3 months and with a minimum of 15 months observation time, from Stanford (n=26, BLTx without BAR) and Copenhagen (n=38, DLTx with complete or incomplete bilateral BAR).*

Survival

Figure 1-3 shows the Kaplan-Meier survival plots at Rigshospitalet versus the total ISHLT survival data (dashed lines) for DLTx (n=66) versus 2822 ISHLT BLTx/DLTx, SLTx (n=69) versus 4199 ISHLT SLTx, and HLTx (n=19) versus 2247 ISHLT HLTx.

The DLTx group is the only group in which BAR was attempted in all cases, while BAR was attempted in 26 SLTx and 10 HLTx patients. With respect to attempted or no BAR, there were no differences in survival between patients with SLTx or HLTx.

Conclusions

Based on experimental studies and clinical experience in patients receiving DLTx (n=66), SLTx (n=27), and HLTx (n=11) with BAR we conclude:

- Up to five bronchial arteries originating from the descending aorta could be identified during surgery.
- The surgical technique for BAR using the IMA conduit was developed to permit safe and reliable BAR of transplanted lungs, be it DLTx, SLTx, or HLTx.
- IMA-bronchial arteriographies showed that the bronchial arteries branch to supply all lung lobes with one or more rami.
- The arteriographic studies allowed development of a nomenclature for the previously uncharted areas of the normal bronchial artery anatomy, based on the pulmonary lobe relation of the arteries.
- Based on the achieved knowledge of the normal bronchial artery anatomy, a classification system was developed for the surgical success after attempted BAR (complete, incomplete, or failed).
- In primary DLTx, 60 % of BAR attempts resulted in complete BAR. BAR failed in five percent of the cases. The remaining patients had varying degrees of incomplete BAR.
- The internal mammary artery was an excellent BAR conduit, with a 100% two year patency. Bronchial vascularity during this period remained unchanged or improved, with no sign of post transplantation bronchial artery disease.
- The bronchial arteries were shown to supply mainly the central structures of the lungs, the central airways, and the hilus area, but they reached all parts, even the most peripheral.
- Bronchial artery flow in transplanted lungs was between 19 and 89 ml/min, corresponding to 0.2 - 1.9 % of estimated cardiac output.
- Ciliary beat frequency or loss of cilia in the bronchi of transplanted single lungs was not influenced by BAR. Bronchial epithelium metaplasia (from columnar epithelium to metaplastic or squamous epithelium) was found only in transplanted lungs without BAR.
- Airway healing after complete and incomplete BAR was good. Bronchial dehiscence was found only in patients with failed BAR.
- The comparison of DLTx patients with BAR from Copenhagen, with BLTx patients without BAR from Stanford University indicated that BAR may postpone the onset of OB.
- DLTx patients who eventually developed BOS had a significantly lower lung function early after the transplantation than patients who

did not develop BOS, indicating that the process resulting in BOS started very early.
- The patient survival rate after LTx with BAR was superior to the reported international experience with LTx without BAR

Our results indicate that DLTx with BAR is a viable alternative to BLTx without BAR.
It remains to be shown whether the good results were exclusively caused by BAR or may have other explanations. However, it is our firm believe that restoring the lungs' normal dual blood supply by BAR contributes to improved outcome after lung transplantation.

Future perspectives for BAR

In a worldwide perspective little has changed concerning the long-term prognosis after LTx since BAR was introduced clinically in 1992. Only a few transplant centers have decided to use BAR in their clinical practice. Only approximately 3% of BLTx/DLTx, and less than 1% of SLTx worldwide, have been performed with BAR.

There are several indications that successful BAR is beneficial to the lungs and to short- and long-term results after LTx. Although BAR does not prevent BOS / OB, it has in no way been excluded as a positive prognostic factor after LTx.

Performing BAR is technically demanding and shows a learning curve. However, even including the early experience, results have been good enough to justify continued use. This should eventually answer the question as to whether BAR will improve long-term results after LTx. To answer this question a large number of patients need to be followed for a long period. Problems to overcome are that randomized studies are difficult to design and multicenter cooperation is needed.

Very little is known about the physiology of the bronchial artery circulation, and its importance to the well-being of transplanted lungs, to the resistance and defense against infection, the development of acute and chronic rejection, recovery after infection, and rejection, etc. The list of unanswered questions is still long, and there is need for continued research to produce the answers.

The pharmaceutical industries are making great efforts, using huge sums of money to improve the pharmacological treatment of transplanted patients, in the belief that pharmacological improvements will be the major cornerstone for improving the patients' survival and quality of life. Time will show whether this prophecy holds true. It is hoped that future research will answer the question as to whether re-establishment of normal blood supply by BAR in LTx will have a similar effect, using only a few sutures and surgical skill.

Dansk resumé

Afhandlingen består af syv originalartikler og en sammenfattende redegørelse omhandlende kirurgiske, anatomiske, fysiologiske og kliniske aspekter af direkte bronkial arterie revaskularisering (BAR) ved kliniske lungetransplantationer (LTx) udført på Rigshospitalet i København i perioden 1992-1998 og publiceret i perioden 1997-1999.

Ved påbegyndelsen af forskningsaktiviteten i 1995 var den tilgængelige litteratur om BAR ved LTx begrænset til fire originalartikler omfattende i alt 29 LTx patienter. I perioden 1995-1998 er yderligere tre originalartikler om BAR ved klinisk LTx publiceret af andre forfattergrupper. Ved afslutningen af resultatindsamlingen (1998) var antallet af LTx patienter med BAR på Rigshospitalet 66 dobbelt-LTx, 27 enkelt-LTx, 11 Hjerte-LTx og een bilateral-LTx. Fraset bilateral-LTx patienten indgår samtlige patienter i større eller mindre omfang i originalartiklerne. De i afhandlingen indgående originalartikler har således i væsentlig grad bidraget til den internationalt tilgængelige viden om BAR ved LTx.

Forskningsaktiviteten koncentrerede sig om følgende emner:

- Udvikling af en sikker og pålidelig procedure for BAR ved LTx.
- Bronkialarteriernes anatomi i donorlungerne.
- Revaskulariseringens holdbarhed over tid.
- Bronkialarteriernes flow volumen og flow fordeling efter LTx med BAR.
- Effekterne af BAR for bronkiernes epitel, herunder ciliernes slagfrekvens.
- De kliniske resultater efter LTx med BAR.

Dette resulterede i følgende hovedkonklusioner:

- Den kirurgiske BAR teknik udvikledes og tillod sikker, pålidelig og hos de fleste patienter komplet revaskularisering af bronkialarterierne ved såvel dobbelt- enkelt- og hjerte-lunge transplantation.
- Den kirurgiske identifikation af bronkialarterierne var pålidelig, men en indlæringskurve kunne registreres.
- Bronkialarteriernes anatomi efter LTx med BAR blev beskrevet og nomenklatur for de ikke tidligere kortlagte dele af bronkialarteriernes forgreninger blev udviklet.
- Arteria mammaria interna blev påvist at være en velegnet fødearterie med en 2-års holdbarhed på 100%. Forekomsten af arteriografisk påviselige bronkialarterier i denne observationsperiode forblev uændret eller tiltog.

- Bronkialarterierne blev vist at forsyne primært de centrale strukturer i thorax, men tillige i mindre grad de mest perifere dele af lungerne.
- Bronkial arterie flow værdier svarende til 0,2 - 1,9 % af estimeret hjerte-minutvolumen blev påvist hos dobbeltlungetransplanterede med komplet revaskularisering.
- BAR havde ikke nogen påviselig indflydelse på ciliernes slagfrekvens eller tab af ciliering i bronkialepitel i transplanterede lunger. Lunge epitel metaplasi blev udelukkende fundet i transplanterede lunger uden BAR.
- Fungerende BAR forhindrer ikke udvikling af bronchiolitis obliterans syndrom og/eller histologisk obliterativ bronchiolitis.
- Sammenlignende studier af dobbeltlungetransplanterede patienter fra Rigshospitalet (med BAR) og bilateralt lungetransplanterede patienter fra Stanford University (uden BAR) antydede at BAR muligvis udskyder tilkomsten af obliterativ bronchiolitis.
- Dobbelt lungetransplantation med BAR er et attraktivt alternativ til bilateral lungetransplantation uden BAR.

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