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Central Message

Bronchial artery revascularization is a safe and reproducible technique that may provide benefits beyond airway healing with a potential of decreasing BOS/CLAD and improve long-term survival.

Abstract (limit 250 words)

The lung transplant community has long ignored the importance of bronchial arterial blood supply. We review relevant history, published articles addressing post-transplant ischemia, and single center reports of lung transplant with bronchial artery revascularization (BAR), followed by details of surgical technique. In our experience, although BAR requires cardiopulmonary bypass (CPB) and there is increased risk of bleeding, ischemic time was shorter and length of ICU and hospital stay was similar. Technical success was achieved in > 95% of cases, which guarantees normal airway healing. Lung transplant with BAR is safe, reproducible, and may provide benefits beyond airway healing with potential for decreasing BOS/CLAD and improving long-term survival. Multicenter study and long-term follow up is needed. (108 words)

Introduction:

Lungs have a dual blood supply from 1) the pulmonary artery and 2) the bronchial arteries (BAs). Approximately 50% of total airway blood supply comes from the BAs, and 50% from the poorly oxygenated pulmonary artery circulation.[1] While the BA circulation represents only 3-5% of total cardiac output, the bronchial arteries can enlarge in response to inflammation, and also provide compensatory gas exchange when the pulmonary circulation fails elsewhere in any region of the lung.[2] BAs originate primarily from the proximal descending aorta, and since they are the only oxygenated blood source for the airways, pulmonary artery and veins (via vasa vasorum), local nerves and mediastinal lymph nodes, they play an important role in airway defense, fluid balance, and lung metabolism. [2-5]

During lung transplant, however, the BAs are routinely sacrificed and ignored due to the perceived technical complexity of BA revascularization. Lung transplant is therefore the only solid organ transplant in which all major arteries to the allograft are not reconnected. A controversial quote by Dr. Robicsek[6] illustrates the issue; - "it makes as much sense to transplant lungs without bronchial arteries as to transplant hearts without coronary arteries." Although this may be an overstatement as many describe outcomes after lung transplantation without BAR as good or even excellent, they certainly are not spectacular and not as good as outcomes after transplantation of other solid organs.

The initial goal of bronchial artery revascularization (BAR) was to improve airway healing. Since the 1990s, the incidence of airway ischemia has decreased due to improved surgical techniques utilizing bi-bronchial anastomosis and better management of immunosuppression, resulting in a lack of enthusiasm to pursue BAR by the greater lung transplant community. However, airway ischemia continues to be a perioperative issue, with estimated incidence from recent reports ranging from 2% - 11%.[7-9] Particularly, patients who are anatomically not a candidate for bi-bronchial anastomosis will require an en-bloc double lung transplant which is reported to have a very high incidence of tracheal complications up to 40%. [10] In addition, there is mounting evidence that compromised microvasculature, suboptimal perfusion and hypoxemia in the transplanted lungs contribute to bronchiolitis obliterans syndrome/obliterative bronchiolitis (BOS/OB) and chronic lung allograft dysfunction (CLAD).[11-13] The lower incidence of tracheal anastomosis issues and CLAD/BOS in heart lung transplant is suggested to be due to preserved coronary to bronchial collaterals.[14, 15] The lack of direct bronchial blood supply likely contributes to several factors which limit the long-term survival after lung transplant, which is still far worse than survival after other solid organ transplants. The limited literature demonstrating benefits of BAR is summarized below. [16]

The largest series of BAR to date demonstrates excellent long-term survival of patients that underwent en bloc double-lung transplant with BAR, with 69% 5-year survival, exceeding the 5 year survival for bilateral

sequential lung transplant without BAR (57%)[17]. As presented at the 2013 International Society of Heart and Lung Transplantation (ISHLT) meeting, 20-year follow-up of patients who had en-bloc double lung with BAR at Copenhagen showed better-than-expected long term survival.[18]

In this report, we summarize the potential benefits of BAR (Online Table 1), review the experimental and clinical literature pertaining to bronchial artery revascularization, and provide a detailed illustrations of the key surgical steps for double lung transplant with BAR.

(Table from reference 16)

HISTORY

Lung transplant with BAR in dogs was described by Metras in the 1950s.[19] Metras sewed a donor aortic button with the BAs to the recipient descending aorta. Animal experiments reported by Mills et al confirmed that BAR improved anastomotic healing.[20] Using Metras' technique, the first technically successful human lung transplant with BAR was reported by Haglin in 1973.[21] The patient had undergone bilateral lung transplant, left lung with BAR and right lung without BAR. The patient expired 11 days after the transplant and autopsy was performed within hours after he had expired and showed that the airway of the revascularized left lung was viable and healing, whereas the right bronchus showed extensive necrosis of all layers.

In the early 1990s, several centers reported series of lung transplant with BAR with promising results (summary below). Subsequently, Pettersson et al. reported results of 106 transplants with BAR in 1994, which is still the largest series published worldwide.

1992, 1996 Courad et al. (Bordeaux, France)[22-24]

Between 1990-1994, 18 patients underwent lung transplant with BAR using saphenous vein graft conduit off the ascending aorta, with follow-up of 22–69 months.[22] The length of surgery increased by 30-40 minutes, but ischemic time was reduced vs. sequential double lung transplant. There were no intraoperative deaths or bleeding related to BAR, but 3 in-hospital deaths (2 urgently transplanted

ventilator dependent patients) and 5 late deaths (2 related to OB). Fourteen of the 18 patients had a post-transplant bronchial arteriogram, which proved that BAR was patent in 11. Normal airway healing was observed in all but one patient, who had limited focal airway necrosis which subsequently healed without further intervention. Five patients with failed BAR all developed obliterative bronchiolitis (OB). The authors concluded that BAR could protect against BOS/OB.

1993, 1997 Daly, Yacoub et al. (Harefield, UK)[25-27]

This series reported outcomes of 9 double lung transplants and 22 single left lung transplants with BAR using internal mammary artery (IMA) conduit. In the double lung cohort, there were 2 reoperations for bleeding from mediastinal tissue and 2 mortalities related to severe graft dysfunction and intracranial hemorrhage, respectively. In the single lung cohort, 3 patients had bleeding, 2 due to chest wall adhesions and 1 from the left IMA->bronchial artery anastomosis. One patient died 6 weeks postop due to severe infection and acute respiratory distress syndrome (ARDS). Twenty-nine of the 31 patients underwent angiograms, all 29 showed patent BAR. Only 1 patient that had visible ulceration at the airway anastomosis which resolved without intervention, and all others had normal airway healing. [25]

1994 Daly, McGregor et al. [28] (Mayo Clinic, USA)

Daly et al. reported the outcomes of 10 single lung transplants with BAR in 1994. There was 1 early mortality due to graft dysfunction. Seven of 9 survivors had patent BAR on postoperative angiogram. There were no airway healing complications noted with median follow up of 13 months [28].

1994-2003 Pettersson et al. (Copenhagen, Denmark)[29-35]

Between 1992 and 1995, 48 double lung, 9 heart-lung, and 5 single lung transplants with BAR was performed, using the internal thoracic artery (ITA) as conduit, similar to the technique described by Dr. Yacoub.[25] BAR added an estimated 20-45 minutes to the procedure for organ procurement, bronchial artery identification, and revascularization. Early bronchial artery reperfusion reduced ischemic time by approximately 1 hour. 5 patients required reoperation for bleeding, 3 from the LIMA anastomosis. 30-day

mortality was 2.1% (1 patient) , 0%, 20% (1 patient), respectively for double lung, heart-lung and single lung. Normal airway healing was seen in 43 patients of the 48 double lung transplant patients. Angiography was performed in 53 patients (43/48 double lung, 6/9 heart-lung, 4/6 single lung) and 50 patients had successful BAR (94%). 2 double lung patients with failed BAR required a left sided pneumonectomy. In patients with successful BAR, 2-year ITA patency was 100%. The overall 5-year survival for double lung transplant with BAR was 63%. The Copenhagen BAR series was later expanded to 68 double lungs, 1 bilateral lung, 27 single lungs, and 10 heart-lung transplants and still represents the largest experience with BAR in the world.

2013 Pettersson, et al. (Cleveland Clinic, USA) [12]

Pettersson and colleagues reported the results of lung transplant with BAR, including comparison to lung transplant cases without BAR with 1:2 propensity-matching. Twenty-seven patients underwent lung transplant with BAR (20 double and 7 single). Patent BAR was confirmed by angiography in 26/27 cases and airway healing was normal in all cases with patent BAR. The single case of failed BAR occurred after en-bloc double lung transplant; central airway ischemia with mucosal sloughing and areas of deep necrosis were seen, but eventually healed without intervention. The BAR and non-BAR groups had similar operative times and overall hospital length of stay, but BAR patients required more reoperations for bleeding ($P<0.002$). These reoperations were primarily related to the ITA-bronchial artery anastomosis. Mortality was 3.7% in both the BAR and non-BAR groups.

2016 McKenzie et al. (Texas Children's Hospital, USA)[36]

McKenzie et al at Texas Children's Hospital reported results of 31 pediatric en-bloc double lung transplants with BAR between 2005–2014 and 88 bilateral sequential lung transplants without BAR. Recipient age ranged from 2 months–20 years. Surgical technique of BAR involved sewing a donor aortic button including the BA origins to recipient descending aorta. There were 2 early mortalities in the BAR group, both unrelated to bleeding or airway ischemia. Ischemic time, cardiopulmonary bypass time, and hospital length of stay was similar between groups. There were no reoperations for bleeding in the BAR

cohort. Airway ischemia was less frequent in the BAR cohort (16% vs. 57%). Survival and freedom from BOS at median follow up 3 years were superior in the BAR cohort (77% vs. 61), 94% vs. 71%), respectively.

SURGICAL TECHNIQUE

The surgical technique is described by figures 1-10 and in the figure legends.

Figure 1: Anatomy of the bronchial arteries.

Schematic drawing of the typical course of the bronchial arteries (BAs). The illustration shows the right inter-costo-bronchial artery (RICBA) with a retroesophageal course and 2 smaller left Bas (LBA). The incise arrow points where to incise the donor descending aorta to preserve the

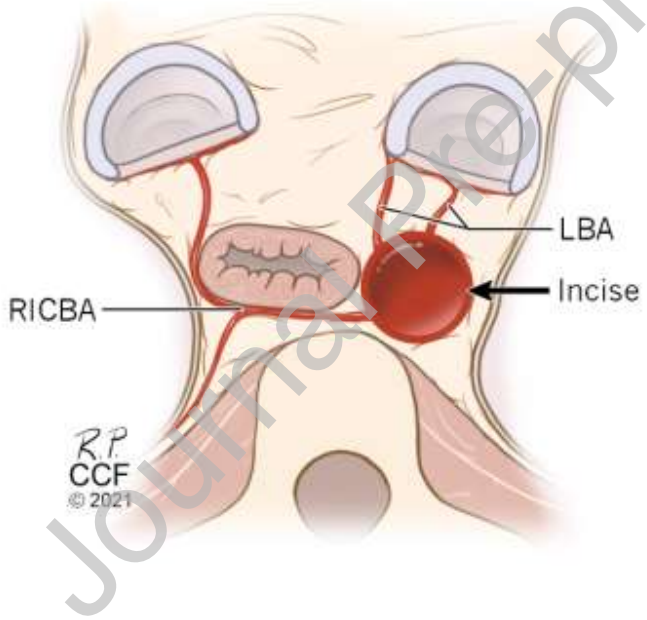


Figure 2: Donor organ retrieval and preparation

The organ procurement team need to be familiar with the anatomy of the bronchial arteries to avoid injury. The donor lungs are removed en-bloc with the trachea, esophagus, and descending aorta in order to preserve the right intercosto-bronchial artery (RICBA) which course behind the esophagus. The trachea and the esophagus are stapled and divided well above the level of the azygos vein. The aorta is divided at the arch and distally at the level of the diaphragm. The distal esophagus is also stapled just above the diaphragm. The lung block is dissected out, staying hard on the posterior chest wall and vertebral column to remove the paraspinal tissue with the block. Usually, the heart has been removed before the lungs are retrieved, hopefully leaving good left atrium cuffs with the pulmonary veins bilaterally and a piece of the main pulmonary artery. We prefer if the pulmonary trunk is divided just above the pulmonary valve. After arrival in the recipient operating room, the lung bloc is held upright with cranial traction of the esophagus. Careful sharp dissection from surrounding mediastinal tissue is carried out caudally staying close to the esophageal adventitial layer to avoid RICBA injury. After the esophagus is removed, mediastinal tissue including the bronchial arteries remains creating a 'tunnel'.

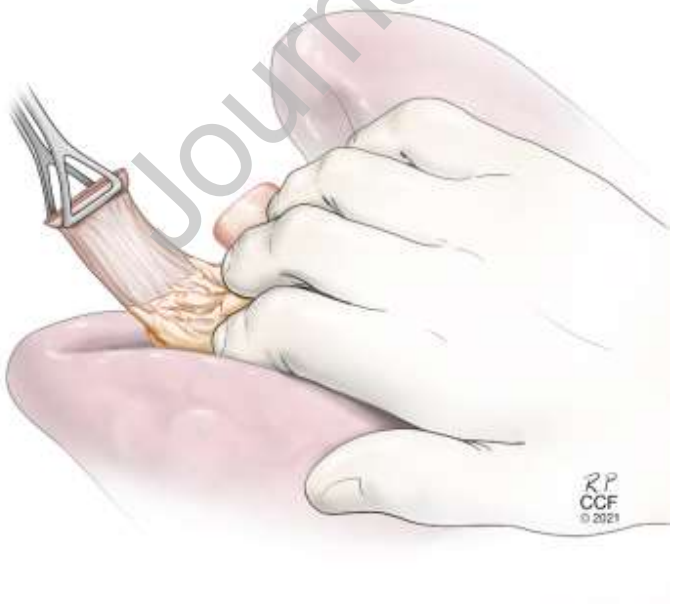


Figure 3: Opening of the donor descending aorta

The descending aorta is opened vertically in the midline on its pleural-covered surface. Orifices of the bronchial and intercostal arteries become visible

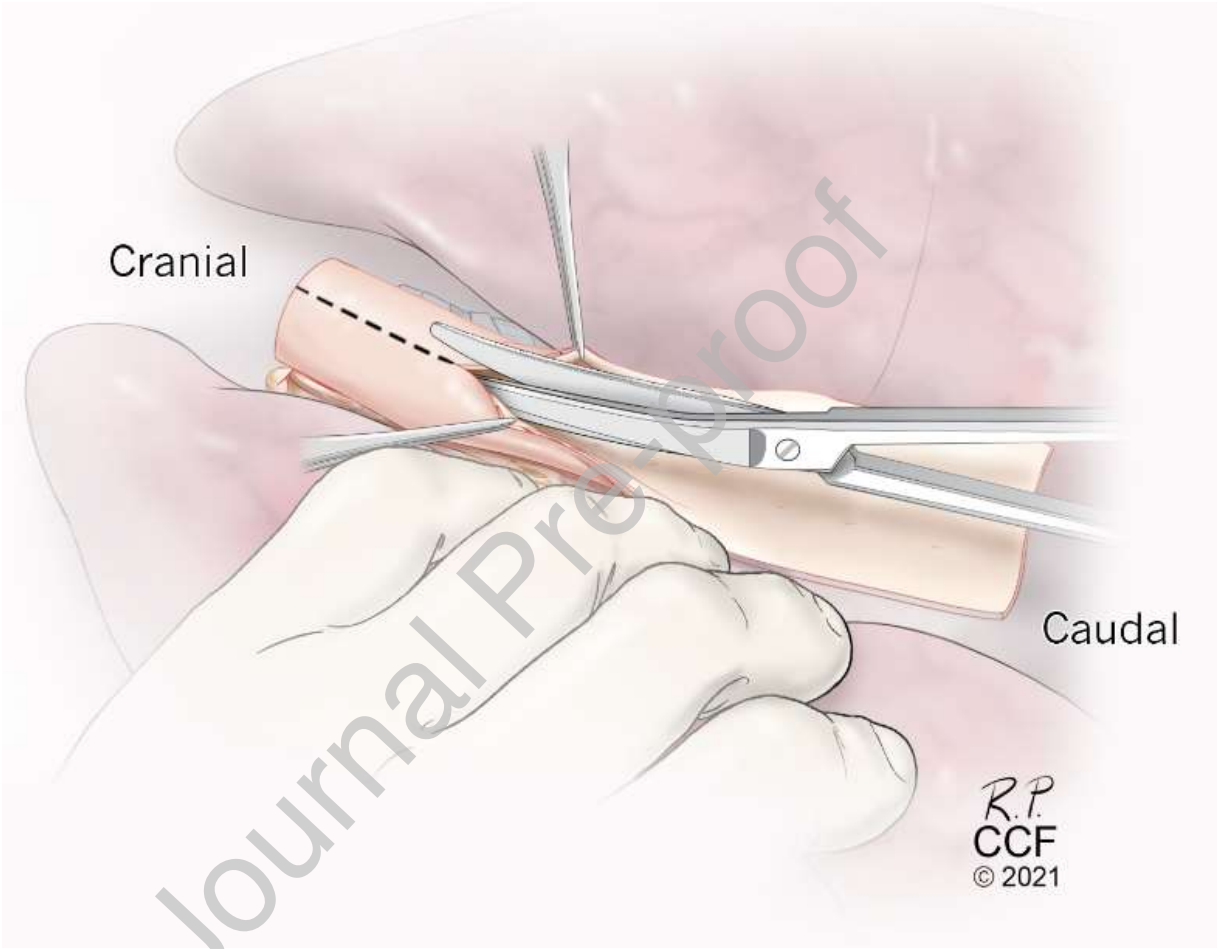


Figure 4 Typical location of the subcarinal artery, RICBA and LBA.

The opened donor descending aorta and the typical location of the bronchial artery orifices is illustrated. The first upper right intercostal branch ostium is usually the largest ostium and most likely to be the ostium of the RICBA. RICBA can be identified in up to 90% of donor specimens according to the study by Schreinemakers et al,[6] but our clinical experience is about 75% to 80%. The left bronchial arteries are found medial and caudally to the RICBA. Often there is a more cranial orifice for a subcarinal or tracheal artery.

Figure 5: Identification of the bronchial arteries

The bronchial arteries are identified by inspection and gentle probing with a 1mm coronary probe. The 'tunnel' where the esophagus was removed is stretched with the left finger inserted to avoid injury to the bronchial artery. This enables to pass a probe safely to identify the course. The intercostal branch taking off from RICBA 1–2cm from the aorta must be identified and clipped to avoid bleeding.

When trimming off excess tissue, great care is taken not to injure the identified BAs. The peribronchial and pericarinal tissue is left intact to avoid jeopardizing the blood supply to the main bronchi and the carina. The donor trachea is divided no more than one ring above the carina.

One large BA is usually enough for complete revascularization. If no convincing BA is identified or the important ones have been damaged, most often the RICBA, BAR should not be performed and the transplant should be done in bilateral sequential fashion with distal bronchial airway anastomoses without BAR.

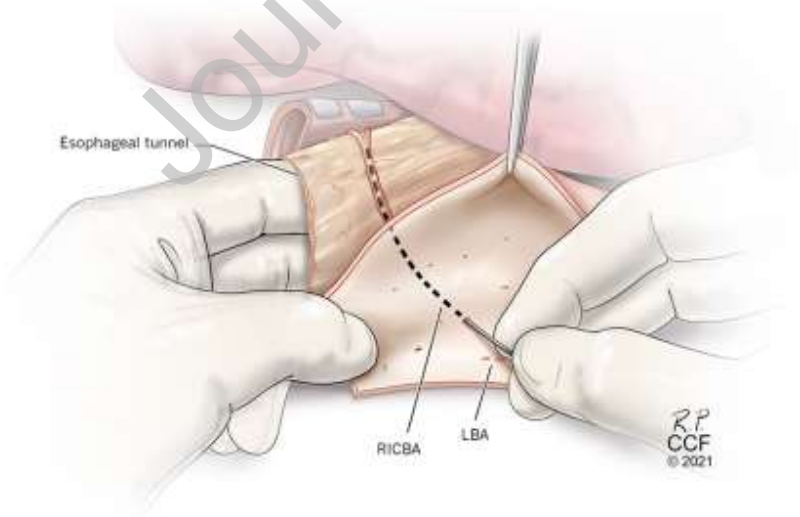


Figure 6: Recipient opening and internal thoracic artery harvest

Median sternotomy is performed and left ITA is harvested in a skeletonized fashion to facilitate sequential anastomosis. This is done before arrival of the lungs; the ITA is left in continuity until patient is heparinized.

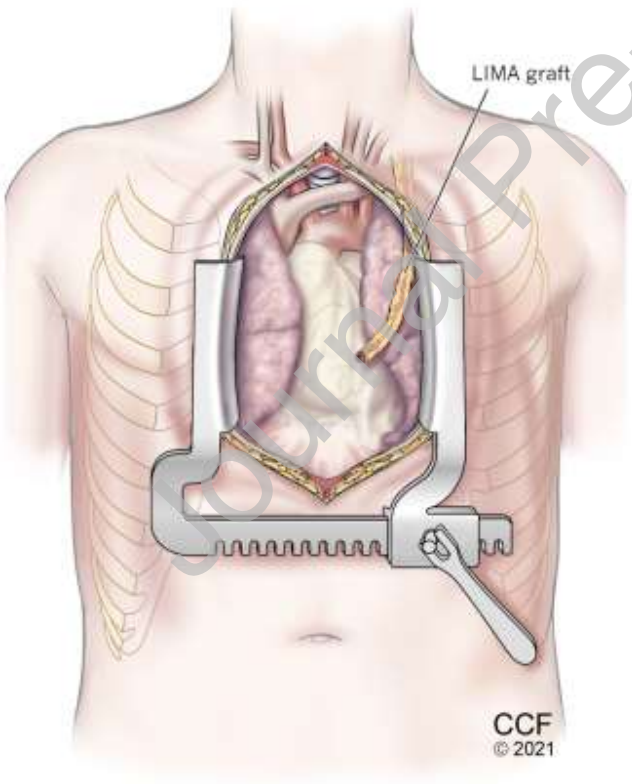


Figure 7 Cannulation for cardiopulmonary bypass and recipient lung removal

The surgeon cannot commit to en-bloc double lung transplantation until the donor block has been examined and useable BAs have been identified. Once the donor lung block is examined and BAs acceptable for BAR are identified, cardiopulmonary bypass is initiated. Cardiopulmonary bypass is mandatory for en-bloc double lung transplantation with BAR. We prefer ascending aortic and bicaval cannulation. The recipient lungs are excised as for bilateral sequential lung transplant and both main bronchi are stapled distally. Once the decision is made to proceed with en-bloc double lung transplant with BAR, the main bronchi are dissected out staying close to the wall and followed back to the carina. The recipient trachea is divided one ring above the carina. Hemostasis of the posterior mediastinum is particularly important. Irrigated bipolar radiofrequency cautery (Aquamantys; Medtronic Inc, Minneapolis, MN, USA) has proven useful in achieving complete hemostasis prior to implant.

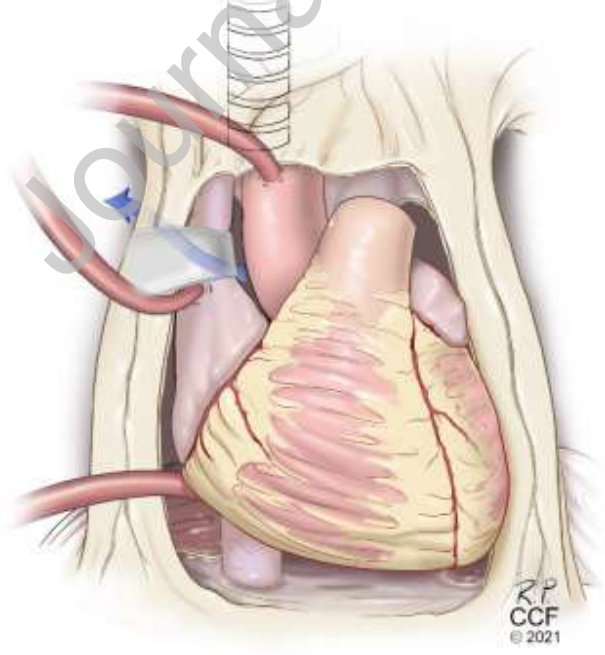


Figure 8: Inserting the donor lung bloc into the pleural cavities

The pericardium is opened to a sufficient extent to allow the donor lung block to be introduced with minimal trauma. The lungs are inserted from behind the heart through the pericardial openings to the pleural cavities. The recipient heart is lifted upward to allow the lung bloc to be passed through the pericardial windows created on both sides behind the phrenic nerves. The lungs are gently pushed through the pericardial openings to their respective pleural space. Since the pericardial openings leading to the pleural spaces are limited in size (particularly on the right), attention must be paid to avoid torsion and proper orientation must be carefully checked.

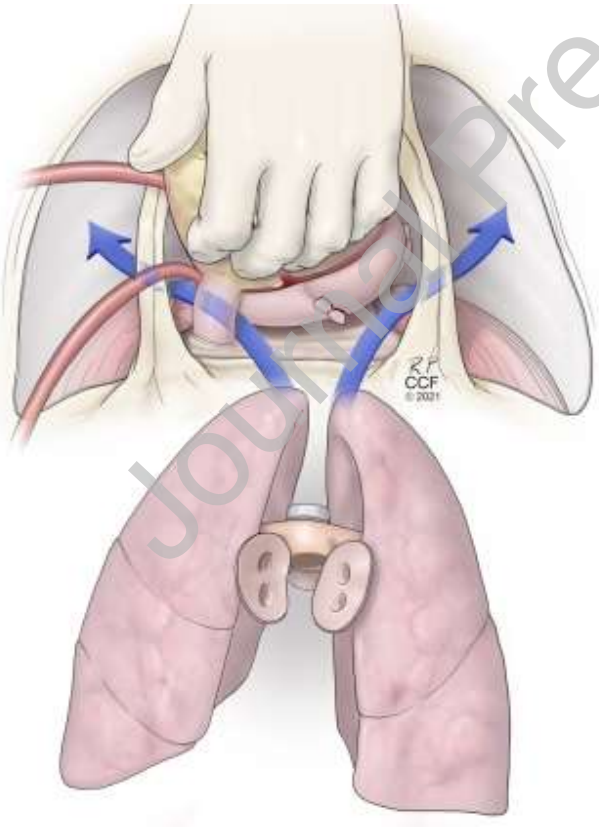


Figure 9: Exposure of the donor descending aorta for the ITA to bronchial artery anastomosis(-es)

After the lung block is inserted, the tracheal anastomosis and pulmonary anastomoses are completed. The left lung is lifted up and rotated towards the right over the heart. The donor descending aorta patch is pulled up and positioned almost anterior to the heart, inside or outside the pericardium depending on the exposure.

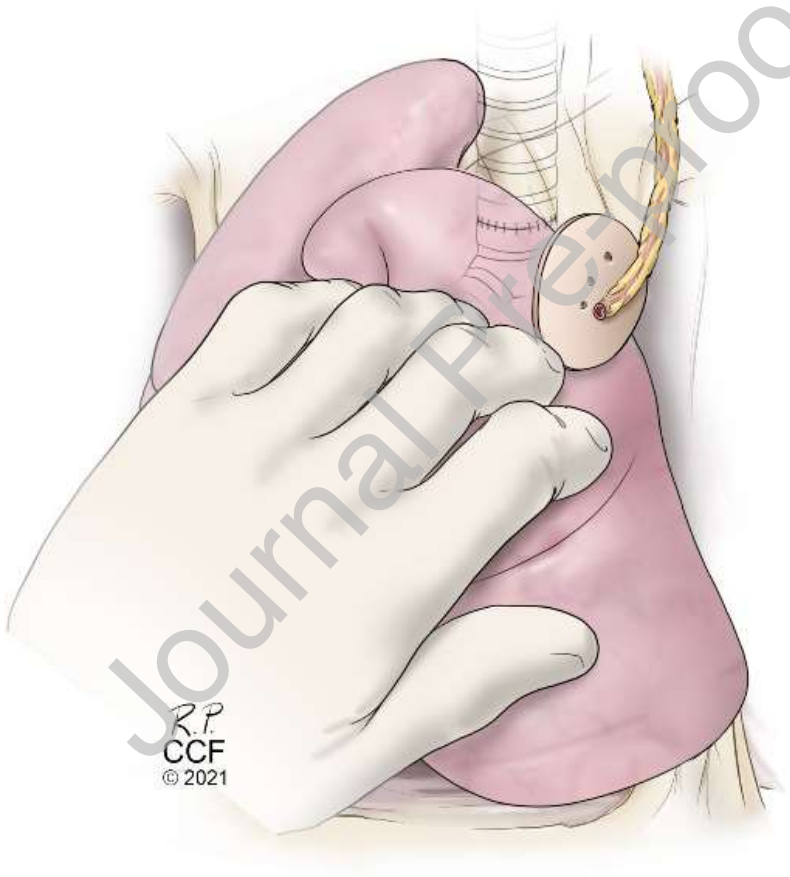
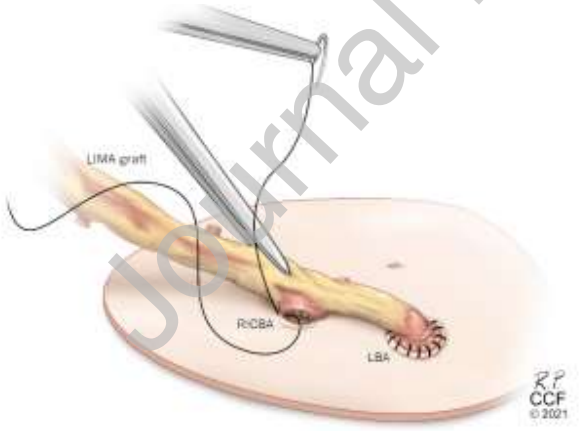


Figure 10: Bronchial artery anastomosis, if more than one done sequentially

The ITA is anastomosed to either a single bronchial artery ostium (if only one is present) or to multiple ostia in sequential fashion. The anastomoses are performed with running 7–0 monofilament sutures. Successful BAR can be immediately confirmed after release of the ITA clamp by observing bleeding from the donor mediastinal tissue and at the tracheal anastomosis. ITA flow can also be assessed with a flow probe. The ITA can be left open, thereby reperfusing the lungs and reducing warm ischemic time. When allowing the left lung to fall back into the left chest, the lie of ITA, anastomosis and donor aorta is checked to ensure a favorable lie with no kinking of the ITA.

Finally, the left atrial cuff anastomoses are completed in the usual running fashion with 4-0 monofilament suture.



Conclusions

Although the collective world experience with BAR is limited, experience from several centers over time suggests that lung transplant with BAR is feasible and safe, with a success rate of > 90%. We present the technical details of en-bloc double lung transplant with BAR using ITA conduit. While our experience suggests that technically successful BAR prevents airway ischemia and ensures normal airway healing, the potential benefits or BAR may extend beyond airway healing. Nobody questions that that restoring the BA circulation is beneficial to the transplanted lungs but Patterson wrote an editorial in annals of thoracic Surgery in 1993 "Airway revascularization: is it necessary?"[37] and was able to convince the lung transplant community that it isn't necessary. However, outcomes after lung transplantation are still not very good and we should ask ourselves if can justify ignoring this obvious possibility of improving outcomes, Patterson's conclusion: "To fully define the value of BAR in lung transplant, a multicenter study including long-term follow up of BAR is required." Time has come to perform this multicenter study.

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