

# Diagnosis and interventions of vascular complications in lung transplant

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**Abstract:** Though rare, pulmonary vascular complications after lung transplantation carry high morbidity and mortality. Knowledge of the normal and abnormal appearance of lung transplant vasculature is essential for timely and appropriate diagnosis and management of complications. Appropriate selection of surgical and endovascular treatments depend on the availability of expertise and requires a multidisciplinary approach to ensure the best outcomes.

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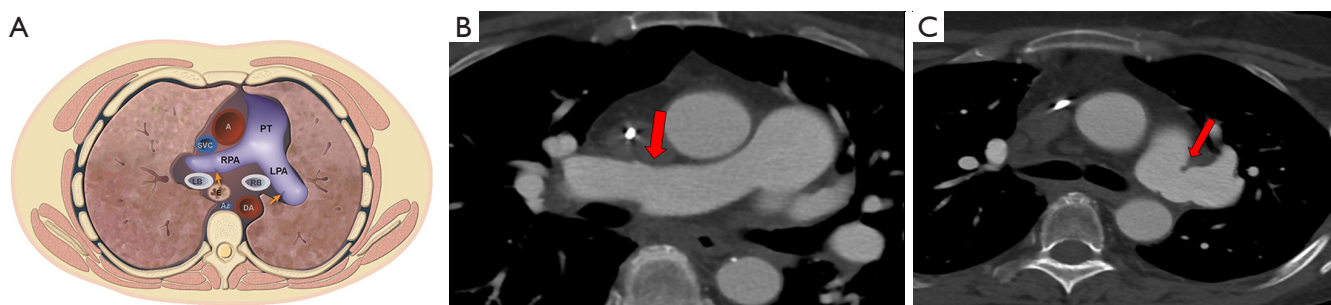
## Introduction

The incidence of lung transplant procedures in the US has progressively increased since the first human lung transplant was performed in 1963 (1,2). Lung transplantation is now an established treatment modality for a broad spectrum of end-stage pulmonary diseases (3). The most common indications for lung transplantation accounting for approximately 85% of all procedures are advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), emphysema due to alpha-1 antitrypsin deficiency, and pulmonary arterial hypertension (PAH). The remaining 15% comprise of end stage lung diseases including sarcoidosis, lymphangiomyomatosis and end stage histiocytosis. The types of lung transplants performed include single-lung transplant, bilateral sequential lung transplants, and heart-lung transplants.

Myriad of pulmonary complications can occur after lung transplantation that can be classified in the following categories: (I) primary graft dysfunction; (II) airway-

related and vascular complications; (III) immediate postoperative complications; (IV) infections; (V) immunological complications (rejection); (VI) neoplasms; and (VII) iatrogenic complications (3). Incidence of various complications varies depending on the time line from the transplant surgery with an overall 42.8% risk of infection and a 10% risk of rejection. Approximately 19.9% of transplant recipients require reoperation (4). The management strategies have been more effective at reducing early complications compared to late, possibly due to improvement in surgical techniques and postoperative care. However, survival beyond the first year is primarily affected by chronic rejection and infections, and the incidence of these complications has not changed substantially in the past few decades.

According to the 2017 registry report by the International Society for Heart and Lung Transplantation (ISHLT), the median survival for all adult recipients is 6 years, with a better survival for bilateral lung transplant (BLT) recipients (5). Recipients with COPD have the best



**Figure 1** An illustration of normal pulmonary arterial anastomosis. (A) Normal appearance the pulmonary arterial anastomoses with thin folds (orange arrows) and no significant change in caliber. CT images (B,C) demonstrate mild caliber change of the right and left pulmonary arterial anastomoses consistent with normal folds (red arrows). PT, main pulmonary artery; RPA, right pulmonary artery; LPA, Left pulmonary artery; A, aorta; SVC, superior vena cava; DA, descending aorta; RB, right main bronchus; LB, left main bronchus; E, esophagus; AZ, azygous vein.

1-year survival (6).

Vascular anastomotic complications following lung transplantation are associated with significant morbidity and mortality, with an incidence ranging from 1.8–5.2% (7,8). Prognosis depends on early diagnosis, type of complication, time elapsed after transplantation, clinical condition of the patient, and selection of the most appropriate therapy (9). We will review and discuss mainly the vascular complications and their management in this article.

### Anastomotic surgical technique

Lung transplantation is a complex surgical procedure usually performed with clamps on the recipient pulmonary artery (PA) and left atrial (LA) cuff, with or without cardiopulmonary bypass (CPB). Vascular injury remains a concern secondary to engagement of the clamp which possibly compromises the integrity of the anastomosis. A “no clamp” technique has been described for vascular anastomosis in lung transplant which is feasible and safe (10). Advantages of the no clamp technique include reduction of warm ischemia and CPB time, and improvement of clinical outcomes. It may also reduce the frequency of post-lung transplantation atrial arrhythmias (10).

Both pulmonary arterial and venous anastomoses are created using a continuous suture technique. The PA is divided proximal to the first arterial branch on both the recipient and donor unless there is a size mismatch secondary to dilated arteries. The arterial anastomosis is more prone to narrowing and kinking when there is poor orientation, severe donor/recipient PA diameter mismatch, or excessive length. The pulmonary venous anastomosis

utilizes a standard LA cuff technique in order to create a wider confluent anastomosis; hence, it is easier to orient the pulmonary venous anastomosis thereby reducing the likelihood of anastomotic suture stenosis or thrombus on the venous side.

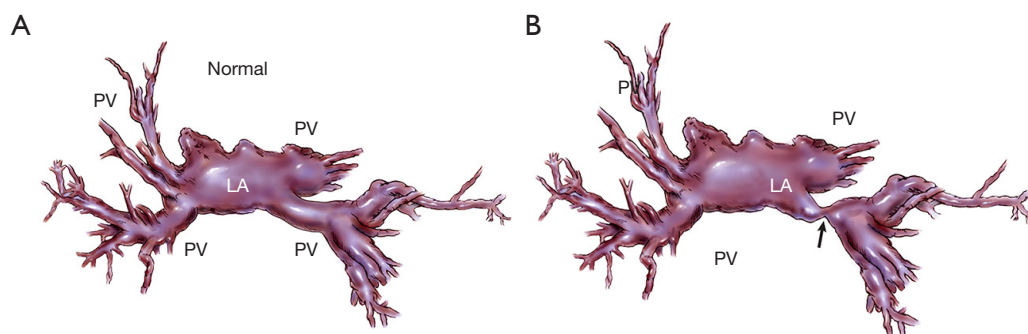
### Vascular complications

Anastomotic stenosis and pulmonary embolism are the most common pulmonary vascular complications following lung transplantation. The incidence of vascular anastomotic complications ranges from 1.8% to 15% (7,8) in different series of studies with a lower incidence of arterial complications (11).

Anastomotic pulmonary arterial stenosis (PAS) was defined by Hausmann in 1992 as an anastomotic diameter of less than 75% compared to the neighboring vessels. It is a rare complication with a reported incidence of less than 2%. A mild degree of stenosis at the arterial anastomosis without hemodynamic significance is a normal finding after transplantation secondary to donor-receptor size discordance or secondary to the suture technique (*Figure 1*).

Pulmonary venous stenosis (PVS) is a rare complication that occurs usually in early postoperative period (first 48 h) after lung transplantation (*Figure 2*). If left untreated PVS may lead to venous thrombosis and transplant failure. The incidence of venous thrombosis is about 15% (11). The inferior pulmonary veins and particularly the left lower pulmonary vein is most commonly involved secondary to their anatomical position and predisposition to suture stenosis (12).

Incidence of pulmonary arterial embolism in patients following lung transplantation has been reported to be



**Figure 2** An illustration of normal and stenotic pulmonary venous anastomosis. (A) Normal appearance of pulmonary venous anastomosis; (B) left inferior pulmonary venous anastomotic stenosis (black arrow). PV, pulmonary vein; LA, left atrium.

ranging from 1–8%. Aside from the transplant surgery itself, other risk factors for venous thrombosis and embolism (VTE) after lung transplant include hypercoagulable state, age, immobility, the presence of central venous catheters, antirejection medications, diabetes and post-transplant pneumonia. It is not uncommon for a lung transplant patient to have multiple of these risk factors placing them in a high VTE risk population.

Five types of vascular complications at the anastomosis have been described. Type 1 is described as kinking of the anastomosis due to excessive length of the donor and recipient segments, distortion of the anastomosis due to inadequate donor vessel length or hilar misalignment. Distortion or kinking of the anastomosis leads to anastomotic narrowing and thrombosis. Type 2 results from transposition of the donor vessel with respect to the recipient. Type 3 is a true stricture of the anastomosis secondary to overtightening or misalignment of the suture line. Type 4 is due to intraluminal obstruction secondary to thrombosis (4A) or dissection (4B). Type 5 refers to extra luminal mass effect associated with the use of omental pedicles (11–14). Conditions that make the vascular anastomosis technically more challenging include previous recipient lung surgery involving the hilum, fibrotic lung disease, female patients (possibly related to small thoracic cavity), small vascular structures, kyphoscoliosis, donor-recipient size mismatch, and lobar transplant (14–17).

### Clinical presentation

Signs and symptoms that should raise suspicion for a vascular complication include persistent dry cough, dyspnea, pulmonary edema, unexplained hypoxia with ventilator dependence, and decline in gas exchange

postoperatively, particularly if associated with pulmonary hypertension and hemodynamic compromise. Entities such as primary graft dysfunction, infection, acute rejection and myocardial dysfunction may present similarly and need to be excluded. Nevertheless, a high index of suspicion for vascular complications is warranted as the clinical features and imaging findings are often non-specific, especially if the symptoms have not improved despite being treated for the above mentioned common postoperative complications. Early identification of PAS is important as improved clinical outcomes have been reported following prompt treatment. Mean time to diagnosis of this complication is about 9 days. Unilateral vascular constriction may remain asymptomatic if there has been a bilateral lung transplant as compared to vascular obstruction in single lung transplant (7). Risk of pulmonary infarction is greatest in immediate post-operative period as there is no bronchial circulation available to provide perfusion due to surgical ligation. Compared to normal lungs, transplanted lungs have only a single source of blood supply and bronchial artery neovascularization takes multiple weeks (18). This means that during this period, the bronchi are supplied by poorly oxygenated blood from the pulmonary arteries in a retrograde fashion through the submucosal plexus at the level of the distal airways. Compromise of the PA during this period results in pulmonary infarction with high associated mortality (19).

### Diagnostic modalities

Various diagnostic modalities are available for diagnosis of vascular complications including echocardiography, intra-operative ultrasound, CT and MRI. The individual role of these modalities depends on the timing of clinical presentation after surgery.

### *Intra-operative diagnosis*

#### **Echocardiography**

Intraoperative anastomotic narrowing can be assessed by direct inspection, or intraoperative imaging with transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). The advantage of using this modality is that it is non-invasive and easy to operate but requires expertise especially for diagnosis of pulmonary venous thrombosis that can be challenging with post-operative altered anatomy (20). Identification and quantification of left inferior pulmonary venous anastomosis in particular may be difficult to visualize with TEE (16,17).

#### **Intra-operative ultrasound**

Felten *et al.* have recently advocated the use of intraoperative contact ultrasound (21). They compared intraoperative TEE and contact ultrasound and found that contact ultrasound produced better left pulmonary arterial recordings whereas TEE was more accurate for venous velocities.

#### **Needle manometry line**

An easy and convenient method that can be incorporated into routine practice is intraoperative direct measurement of pressure gradient across the anastomosis at a period of hemodynamic stability with a needle manometry line. This process allows immediate surgical correction in case of a high pressure gradient across the vascular anastomosis (7).

### *Post-operative diagnosis*

#### **Radiograph**

Imaging with chest X-ray may show pulmonary edema, with nonspecific opacities and /or pleural effusion.

#### **Ventilation-perfusion (V/Q) scan**

A V/Q scan does not allow for intraoperative correction, and has a very limited role. In the post-operative period, A V/Q scan may show absent perfusion and ventilation in lung infarction secondary to pulmonary arterial occlusion and is useful in a setting where contrast is not administered for CT.

#### **CT**

Contrast enhanced CT (CECT) imaging is a readily available non-invasive modality that allows more accurate postoperative evaluation of both arterial and venous stenosis, especially with post-processing techniques that include multiplanar reformations (MPRs), volume rendering, and

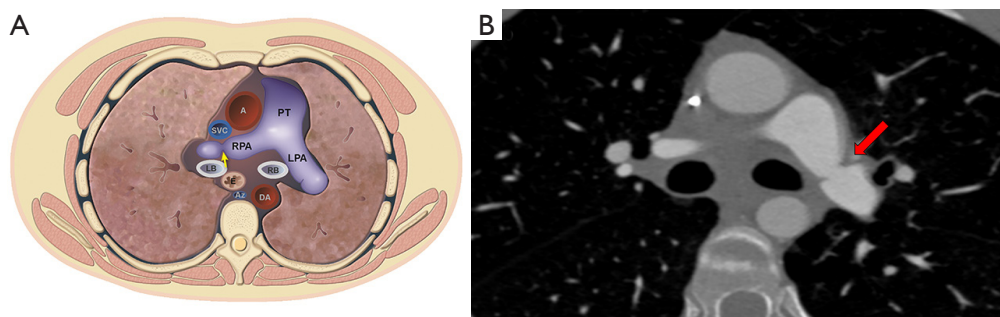
minimum- and maximum-intensity-projection images (22). It is important to direct the CT protocol beforehand as administration of IV contrast in the immediate post-operative period may have unwanted consequences and close collaboration and discussion with the transplant team is an important part of workflow in the management of these patients. For CT pulmonary angiography (CTPA), a volumetric scan is recommended on a multislice CT scanner using automatic tube current modulation and thinnest collimation available. Automated bolus tracking technique can be used to determine the scanning delay and approximate 75–100 mL of nonionic contrast is administered at a rate of 4 mL/s using a power injector. In addition to the assessment of the extent and degree of stenosis, CT also provides information about the lung parenchyma, distal vasculature, collateral vessel, airways, and pleural space. The 3D volume rendered angiographic reconstructions are useful for pretreatment planning. Normally on CECT, vascular sites of anastomosis are visualized as 1–2 mm folds on the walls of the blood vessels without a significant reduction in the diameter (*Figure 1*) (23). Significant change in caliber of the pulmonary vessel is an important indicator of stenosis (*Figures 3,4*). In cases of pulmonary embolism, intraluminal filling defects and abrupt cutoff of vessels are important indicators of acute pulmonary embolism. Multiplanar reconstructions and maximum intensity projection (MIP) images aid in differentiating mucus-filled airways or lymph nodes from pulmonary emboli. The multiplanar capability is also useful in determining success of treatment on follow up scans.

#### **MR angiography (MRA)**

MRA is an important alternative to CTPA is an important non-ionizing alternative to CTPA in younger patients where radiation remains a concern. Advancement in MRI technology including view sharing, parallel imaging and time-resolved MRA, have shortened the acquisition times and have led to increased use of MRA for the primary diagnosis of PE as compared to longer acquisition times, limited volumetric coverage and lower spatial resolution than CTPA in the past years.

The most important sequences in a pulmonary CE-MRA protocol are those acquired after the administration of an intravenous (i.v.) contrast agent and acquired using a rapid three-dimensional (3D) spoiled gradient-echo sequence. The vascular phases of pulmonary CE-MRA, enhance the pulmonary arterial system to facilitate identification of intraluminal filling defects. Non-contrast MRA using bright blood balanced steady-state free-precession (bSSFP)





**Figure 3** Pulmonary arterial anastomotic stenosis. (A) Right pulmonary arterial anastomotic stenosis with significant narrowing and poststenotic dilatation (yellow arrow); (B) left PA anastomosis with moderate stenosis is seen on contrast enhanced CT (red arrow). PT, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery; A, aorta; SVC, superior vena cava; DA, descending aorta; RB, right main bronchus; LB, left main bronchus; E, esophagus; AZ, azygous vein.



**Figure 4** Pulmonary venous anastomotic stenosis. Non-contrast CT image demonstrates a hourglass deformity of the right pulmonary vein (red arrow) in a patient presenting with pulmonary edema and arterial hypertension three months after lung transplant consistent with pulmonary venous stenosis.

sequence are more widely used for assessing pulmonary arteries. Non-contrast bSSFP examinations perform comparably with CE-MRA when evaluating the central and lobar pulmonary arteries (24). A post-contrast T1 weighted spoiled gradient recalled echo (SGRE) acquisition with fat saturation can be of additional advantage in assessment for other pathology in the mediastinum and chest wall.

Dedicated perfusion imaging can also be accomplished using dynamic contrast-enhanced MRI sequences that can appraise qualitative and quantitative perfusion of the lung parenchyma and add to the functional significance of a perfusion defect (25).

### Pulmonary angiography (PA)

Although routinely used prior to 1995, PA is now reserved for instances in which a catheter-based intervention may be required and remains the most commonly used

confirmatory modality. PA is selected with a pigtail or an angled pigtail catheter via common femoral or internal jugular vein approach. Comprehensive evaluation includes pulmonary arterial pressure measurements followed by pulmonary angiogram in multiple projections.

PA demonstrates filling defects consistent with thrombus, either at the level of the anastomosis or peripherally. In cases suspected or known to have large pulmonary embolism or severe PAH, an initial hand injection of contrast material is the preferred option.

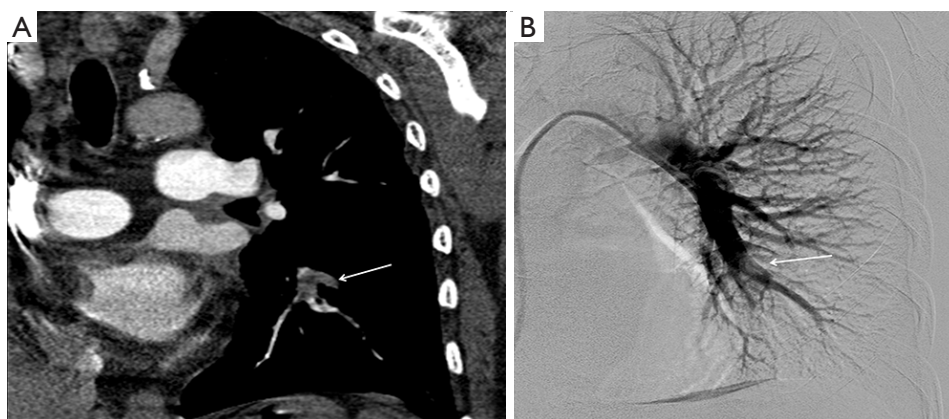
Arterial anastomotic stenosis is well characterized on the pre-procedural CT scan and helps in planning for subsequent intervention. Findings of anastomotic stenosis on angiogram include change in vessel caliber to complete stenosis. Pressure measurement with a gradient across the area of stenosis is useful, especially when the findings of stenosis are equivocal. Additionally, pressure gradient measurement is an important parameter to assess the response during therapy. Based on the vessel caliber immediately central to the stenotic area, balloon dilatation and angioplasty are planned. Evaluation of venous anastomosis requires delayed imaging to result in opacification of the pulmonary veins whereas interventions at this location require trans-septal access. It is very important to weight the treatment benefits with the risk of rupturing the friable anastomosis, especially in the immediate and early post-operative periods.

## Treatment

### Management of complications

#### Immediate

Mild anastomotic narrowing may be treated conservatively,



**Figure 5** Pulmonary thromboembolism complications post lung transplant. Coronal CT (A) and pulmonary arteriogram (B) demonstrate segmental filling defect within the left lower lobe (white arrows) in a post lung transplant patient consistent with thromboembolism.

particularly in the setting of bilateral lung transplant. However a significant stenosis at the arterial or venous anastomosis that compromises the graft and results in clinical deterioration requires immediate intervention. Open interventions to salvage the transplanted lung carry a significant risk and limited reports are available on success rates on open repair of PAS. Ischemic reperfusion injury to the donor organ secondary to vascular clamping during the revision surgery is associated with increased postoperative morbidity, and complications (15,26,27).

Significant anastomotic narrowing can also be treated by catheter based intervention or surgical revision. Endovascular versus surgical treatment is guided by the time that has elapsed after the anastomosis to diagnosis, anatomy of the lesion, clinical condition of the patient and ability to tolerate another intervention in addition to available expertise and experience.

For vascular anastomotic thrombosis, anticoagulation with heparin and close clinical monitoring should be the initial management. Severe thrombosis with potential for graft infarction may necessitate surgical intervention, but endovascular interventions are also an option with various thrombectomy devices and techniques (chemical, mechanical, aspiration, etc.) available and may be used based on individual preference and expertise. Catheter directed thrombolysis (CTD) with tissue plasminogen (tPA) can be performed with catheters across the area of thromboembolism with close monitoring of vitals and coagulation parameters. CTD provides maximum local lytic dose and decreases the systemic lytic dose, thereby offering the advantage of increased lytic efficacy and decreased bleeding risk compared to systemic thrombolysis (28).

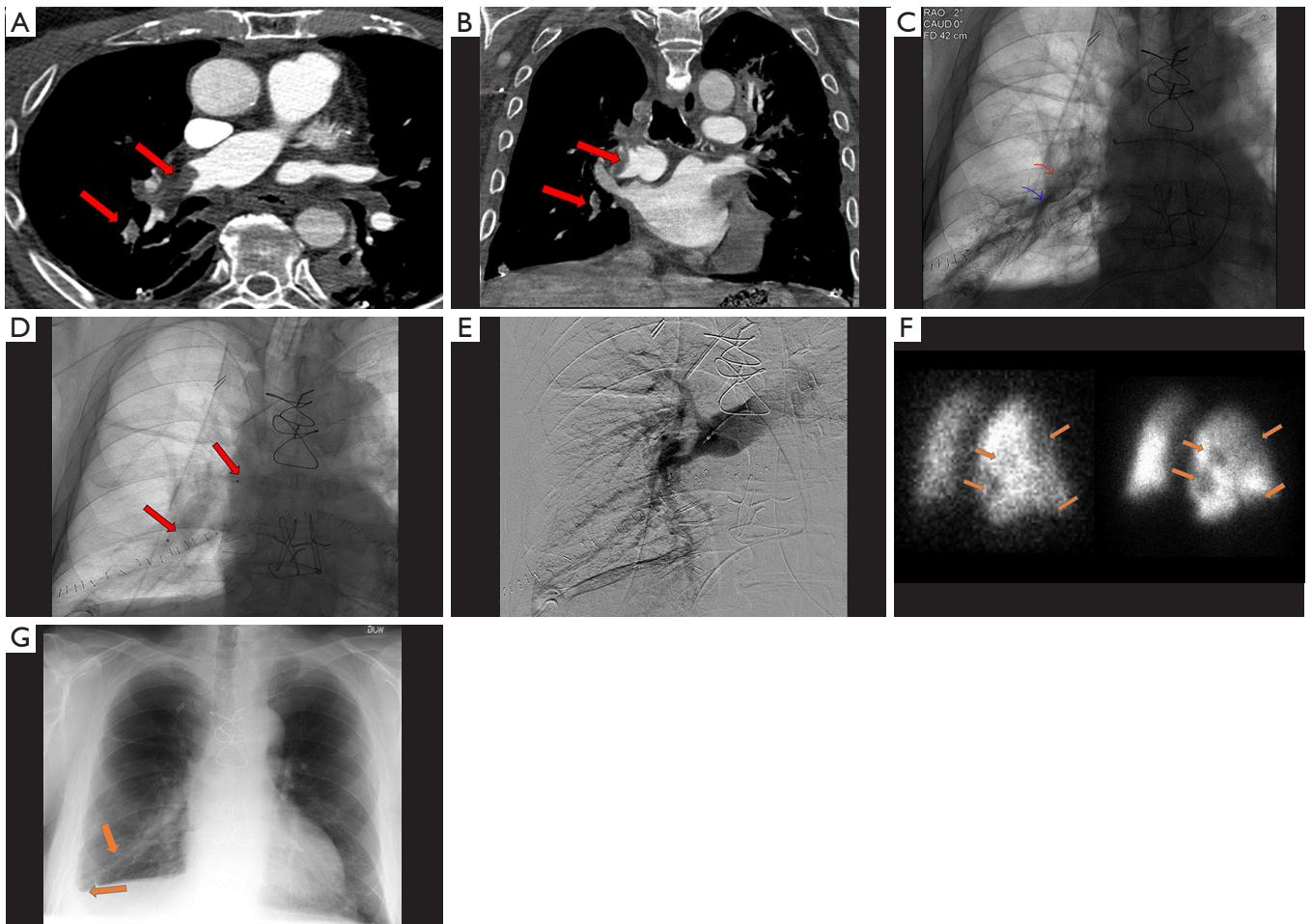
CTD treatment in lung transplant patients is similar to treatment of pulmonary embolism in non-transplant patients except for careful consideration of friable anastomosis, and a relative contraindication in the immediate postoperative period (*Figures 5,6*). Despite this relative contraindication, the risk of bleeding must be weighed against the risk of graft loss and death.

#### Intermediate

In the first 2 weeks after transplantation, it remains debatable as to the preferred approach for treatment of vascular anastomotic narrowing and thrombosis. A surgical approach is generally favored as the integrity of the anastomosis is friable given the short interval time from the time of surgery. Surgery may also be necessary in cases when there is inversion of the donor vessel with respect to the recipient. The transplanted lung is cooled on CPB and cold pulmoplegic solution is utilized to prevent warm ischemia and infarction. Successful treatment is attributed to stabilization and preventing twisting of the anastomosis. In the scenario where the anatomy is favorable and expertise is available, an endovascular treatment with careful balloon dilatation and stenting is an option with careful attention to friable post-operative vasculature, and risk of complications including stent migration, thrombosis, restenosis and embolization.

#### Delayed

For cases diagnosed in the delayed (several weeks) postoperative period, multiple groups have reported success with endovascular techniques and interventions (29-32). Excellent functional and anatomic outcomes with low



**Figure 6** Endovascular treatment of pulmonary thromboembolism in a post lung transplant patient. Axial contrast enhanced CT (A) showing a normal right pulmonary artery transplant anastomosis with acute-appearing thrombus immediately distal to the anastomosis extending into lobar branches (red arrows). Coronal CTA (B) showing a normal right pulmonary artery transplant anastomosis with acute-appearing thrombus immediately distal to the anastomosis extending into lobar branches (red arrows). Fluoroscopic spot film (C) showing an expansile filling defect in the right inferior pulmonary artery (red arrow) with distal stasis during gentle contrast injection (blue arrow). Fluoroscopic spot film (D) showing the position of a 10-cm infusion length thrombolysis catheter (red arrow) for continued thrombolysis infusion therapy. Right pulmonary angiogram (E) was obtained after 12 h of thrombolysis. Note that although there are residual filling defects, there is interval improved flow. Patient was subsequently treated with systemic anticoagulation. Ventilation and perfusion scan (F) performed 6 months after thrombolysis shows matched non-segmental defects in the right upper and lower lobes, sequelae of prior thromboembolism (orange arrows). CXR (G) at 6 months post lysis shows residual scarring in the area of prior infarcts and a chronically blunted right costophrenic sulcus (orange arrows).

mortality and morbidity rates after percutaneous angioplasty with or without vascular endoprosthesis were reported for severe anastomotic stenosis of the PA (30,33,34). Most pulmonary arterial lesions require stent placement due to the elasticity of the lesions, although angioplasty without stent placement is also an alternative option (9). A second stent may be deployed partially inside the first one to cover

for insufficient length over the lesion with good short-term functional and anatomic outcomes. For persistent or recurrent stenosis, deployment of a balloon-mounted stent is preferred over a self-expanding stent. No specific guidelines exist regarding the follow up after endovascular intervention. Short term anticoagulation and/or antiplatelet therapy is the cornerstone for maintaining patency of the



stents. Follow up imaging utilizing a CECT or angiogram can be obtained at short term intervals or depending on the clinical symptoms. Nevertheless, presence of an endovascular stent may make repeat lung transplantation cumbersome. Extensive dissection towards the hilum is required to ensure that clamp can be placed beyond the stent and allow safe removal of the stent.

In patients with complete venous obstruction, repeat surgery, re-transplantation or lobectomy for double lung transplantation may be required. However, if the condition of the patient is stable and a favorable anatomy is identified, angioplasty with dilation and endovascular stent implant has been shown to be successful (15).

### Conclusions

Vascular complications after lung transplantation are rare but can result in high mortality and morbidity if left untreated. The arterial anastomosis is more prone to complications of stenosis and thrombosis compared to venous anastomosis due to surgical technique and pathophysiology. Since the signs and symptoms are non-specific, a high index of suspicion is needed to prevent a missed diagnosis. Diagnosis is primarily via echocardiogram or CTA imaging. CTA has additional benefits of advanced post-processing capabilities and being able to image the lung parenchyma. Surgical and endovascular interventional techniques have both demonstrated successful salvage of the organ and the patient in treating post lung transplant complications. Endovascular stent placement for transplant related arterial stenosis has a low mortality and morbidity with successful functional and anatomic outcomes in the short term.

PE is problematic due to compromised bronchial circulation with possible infarction and graft loss and is associated with a high mortality. Catheter directed lysis is an alternative to embolectomy/surgical revision with the need to weigh in bleeding risks and friable anastomosis compared to re-operative risks. Both surgery/re-transplantation and intervention techniques on vascular structures after lung transplantation require careful multidisciplinary evaluation and high procedural expertise.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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