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Surgical Treatment of Pulmonary Hypertension

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Introduction

Pulmonary hypertension (PH) is not a pleasant condition for surgeons, and in general, PH becomes a contraindication to many operations, or it makes the operation a lot more complex. The increased morbidity and mortality that PH causes and the additional requirement of monitoring using a pulmonary artery catheter makes many people uncomfortable with PH of any cause. However, there are some situations where PH itself is amenable to surgical cure or surgical palliation. Many of the diseases classified under the WHO Group IV at the 6th World Symposium on Pulmonary Hypertension (WSPH) held at Nice in 2018[1] including chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions such as malignant or nonmalignant tumors, congenital pulmonary artery stenosis, and parasitosis will require surgical intervention as a diagnostic, therapeutic, or palliative procedure. Besides, these surgical or interventional palliative procedures such as the reversed Potts shunt or atrial septostomy have a beneficial effect on right-ventricular (RV) failure and prevention of sudden death in other WHO PH groups as well. Reversed Pott's shunt has been given an IIb class of recommendation as destination therapy or as bridge to bilateral lung transplantation in children with end-stage pulmonary artery hypertension (PAH).[2] Finally, lung transplantation or combined heart-lung transplantation is also to be mentioned as surgical treatment for PH. For the purpose of this chapter, the discussion will be limited to aspects of CTEPH.

Definitions

CTEPH is a form of precapillary pulmonary hypertension; it is a complication of acute pulmonary embolism that occurs in approximately 3.5% of patients who develop acute pulmonary embolism.[3] The 2015 European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of pulmonary hypertension stated, "The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation in order to discriminate this condition from subacute PE. These findings are mean pulmonary artery pressure (mPAP) >/= 25 mm Hg with pulmonary artery wedge pressure (PAWP) </= 15 mm Hg, mismatched perfusion defects on lung scan, and specific diagnostic signs for CTEPH seen by multidetector CT angiography, MR imaging, or conventional pulmonary cine angiography, such as ring-like stenoses, webs/slits, and chronic total occlusions (pouch lesions or tapered lesions)."[4] Some patients may have similar perfusion defects and symptoms but show no PH. This condition was referred to as chronic thromboembolic disease (CTED).[5] Since this definition, the threshold of mPAP for diagnosis of PH has been revised. In 1961, a report by the WHO Expert Committee on chronic cor pulmonale mentioned that the mPAP doesn't normally exceed 15 mm Hg and is not affected by age and never exceeds 20 mm Hg.[6] The first WSPH held in Geneva in 1973, organized by WHO[7] defined PH as mPAP of =/>25 mm Hg measured by right heart catheterization (RHC) at rest, in supine position. This definition was empirical and defined arbitrarily. In 2009,[8] data from 1187 normal subjects were analyzed from 47 studies. The mPAP at rest was found to be 14.0 +/− 3.3 mm Hg. This mPAP of 14 mm Hg and two standard deviations above this as the upper limit of normally raised mPAP above 20 mm Hg were taken as cutoff values to define pulmonary hypertension, and this is no longer arbitrary since there is scientific reasoning to it. For defining precapillary pulmonary hypertension hemodynamically the 6th WSPH also made the requirement of having a PAWP of </= 15 mm Hg and a pulmonary vascular resistance (PVR) of 3 woods units (WU).[1] The PVR threshold was further revised to 2 WU in the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.[9] The European Respiratory Society in its statement on CTEPH in 2021 proposed the term "chronic thromboembolic pulmonary diseases (CTEPD)" to include all symptomatic patients with or without PH having this disease. The term "CTEPH" was maintained for those who have PH at rest. PH in this setting can be from proximal organized thrombotic obstruction, which can also be due to secondary microangiopathy affecting vessels smaller than 500 micrometres.[10]

Diagnosis

Among the various etiologies of pulmonary hypertension, CTEPH is the only condition that has a curative treatment option, though it may be debatable if one is entirely cured of this disease with treatment. Therefore, it is important to establish the correct diagnosis in this group of patients who have pulmonary hypertension. Patients may present with exercise intolerance, shortness of breath, signs and symptoms of right heart failure. The diagnosis of pulmonary hypertension is usually first made on echocardiography showing raised systolic pulmonary artery pressure (sPAP). In the evaluation and categorization of PH, usually the first diagnostic test aimed at excluding or confirming CTEPH would be a ventilation-perfusion scan (V/Q). A negative V/Q scan effectively rules out a diagnosis of CTEPH; therefore, as a screening tool, it remains the most effective method of imaging. A high-quality computed tomography (CT) pulmonary angiogram (CTPA) is also quite good at diagnosing CTEPH; however, it should be kept in mind that a negative CTPA does not completely exclude CTEPH as very distal disease can be missed by conventional CTPA. Though dual-energy CT and magnetic resonance imaging (MRI) can also be useful screening tools with some advantages, they do not replace V/Q scan in today's clinical practice.[10]

Echocardiography

Besides being the usual modality for the first diagnosis of PH, it can also look for the structure and function of the heart that is relevant to PH. The commoner cause of PH is left heart disease, and echocardiography can diagnose this with good specificity. Echo also helps to determine the function of the right heart and the degree of tricuspid regurgitation (TR). Though the fibrous clots in the pulmonary arteries are rarely seen on echo, clots in the right-sided cardiac chambers can be demonstrated.

Computed Tomography Pulmonary Angiogram

It is the go-to imaging modality in most centers and might replace angiogram to assess operability and define the disease anatomically to provide a roadmap for pulmonary thromboendarterectomy (PTE). Besides the anatomical definition, CT also demonstrates the condition of the lung parenchyma and the presence or absence of systemic-pulmonary collaterals. These collaterals are an important determinant of operability and can help to distinguish from WHO Group 1 PH with in situ thrombosis. The collateral flow can be up to 30% of the systemic blood flow in CTEPH but rarely exceeds 1% of systemic blood flow in WHO Group I PH.[11,12] CT is also helpful to differentiate CTEPH from other conditions that may mimic it, such as pulmonary artery sarcoma, vasculitis, fibrosing mediastinitis, and as mentioned earlier in situ thrombosis.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) when used with maximum intensity projection (MIP) can demonstrate the pulmonary arteries well. In addition, MR has the advantage of being able to assess the function of the right ventricle and perfusion in the lungs. It is also useful as a follow-up tool following surgical or interventional therapy.

Cardiac Catheterization and Catheter-Based Angiography

In most CTEPH centers all the patients undergo cardiac catheterization before undergoing treatment for the disease. Right heart catheterization (RHC) is done and all the hemodynamic measurements are obtained. The mPAP and PVR are determined only on RHC. Echo estimates of sPAP can be inaccurate in this setting; mPAP and PVR and PAWP which are required for defining and categorizing PH are available only through RHC. It should be remembered that measurement of PAWP may not always be accurate in CTEPH due to obstruction of the pulmonary arteries. In order to rule out left heart disease, left ventricular end-diastolic pressure may need to be measured. Historically, catheter-based angiography was used as the roadmap for surgical PTE, though currently, some centers use CTPA for that purpose; digital subtraction angiography is also a good alternative, and some consider it to be the gold standard in CTEPH imaging. Additional dye injections are done in the coronary arteries, bilateral internal mammary arteries, and the descending thoracic aorta to look for and demonstrate systemic–pulmonary collaterals and to rule out coronary artery disease. During the capillary phase of the pulmonary angiogram, poor subpleural perfusion may indicate small vessel disease and therefore increased mortality.[13] In the setting of balloon pulmonary angioplasty (BPA), the lesions in CTEPH were classified by the lesion morphology as type A through E, ring-like lesion was called type A, web lesions type B, subtotal and total occlusions types C and D, respectively, and a tortuous lesion was described as type E.[14] Advanced imaging combined with high computing power has led to the application of artificial intelligence in image analysis using machine learning. A model has been developed to better predict patient outcomes in various PH groups including CTEPH.[15,16] This will be a space to watch for in the next decade, particularly if quantum computing becomes more accessible and is used more widely in healthcare analytics. At the moment, it is difficult to predict accurately which patients have significant microvascular disease in addition to surgically accessible obstructive disease (**Fig. 15.1**).

A multidisciplinary team consisting of cardiologists preferably those who have the ability to perform BPA, PH specialist pulmonologists, cardiac imaging specialists, and an experienced PEA surgeon should review the patient data and imaging in detail and make an individualized plan for each patient which may include surgical, interventional, medical, or a combination of various modalities whichever is appropriate for the given patient.

Patients with no history of deep vein thrombosis (DVT), having signs of right heart failure, in functional class IV, having no disease appreciable in the lower lobes, and showing inconsistencies on various imaging modalities, particularly if PVR is >15 WU and out of proportion to the amount of obstruction seen on imaging and having high PA diastolic pressure, are thought to be a high-risk group.[5]

The University of California San Diego (UCSD) group has proposed a surgical classification based on the level where the disease starts with level 1 starting in the main pulmonary arteries, level 2 at the level of the lobar, level 3 (**Fig. 15.2**) at segmental level, and level 4 at subsegmental level. Level 1C refers to complete obstruction of one of the branch of pulmonary arteries (**Fig. 15.3**) and level 0 refers to having no thromboembolic disease in either lung.

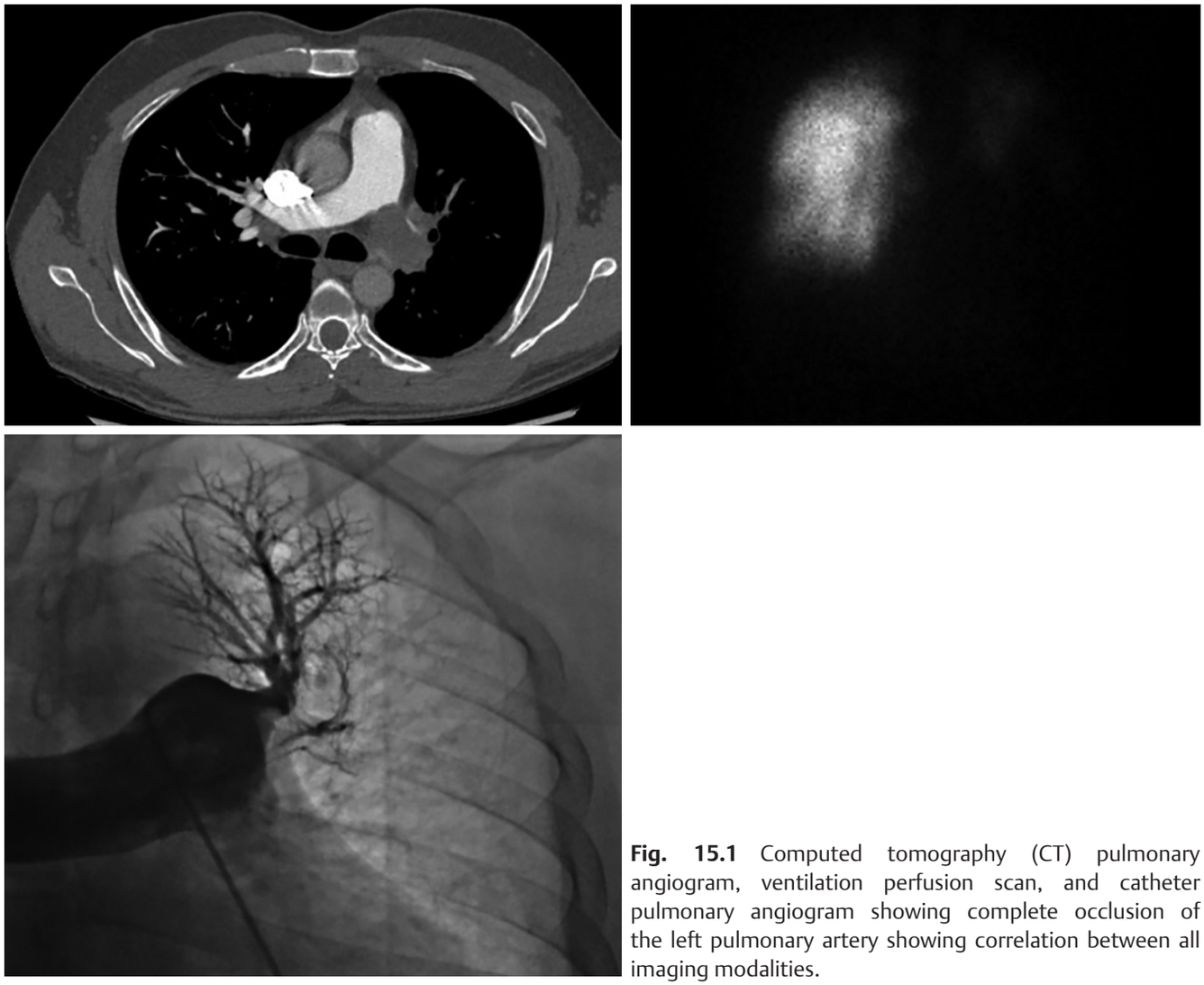

Fig. 15.1 Computed tomography (CT) pulmonary angiogram, ventilation perfusion scan, and catheter pulmonary angiogram showing complete occlusion of the left pulmonary artery showing correlation between all imaging modalities.

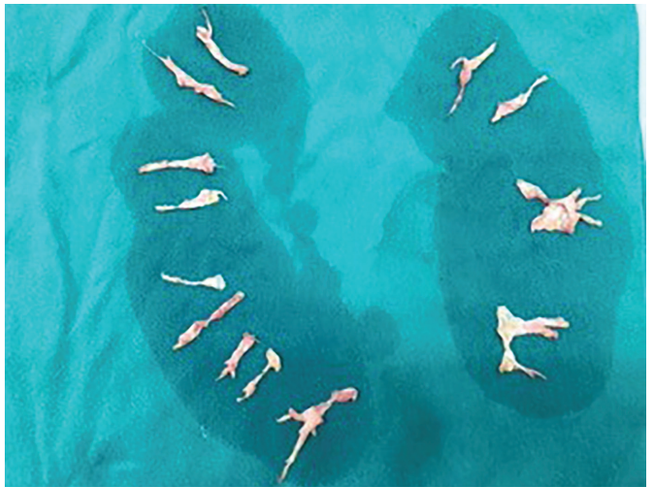

Fig. 15.2 Pulmonary thromboendarterectomy (PTE) specimen showing level 3 disease commencing at segmental level extending distally.

Treatment

General Treatment

All patients who have been diagnosed to have CTEPH should be on lifelong anticoagulation. This has been traditionally done with Vitamin K antagonists (VKA); however, novel oral anticoagulants (NOACs) are increasingly replacing VKA, though most CTEPH centers continue to use VKA. NOACs are not recommended for use in patients who have antiphospholipid antibody.[17] If the patient is hypoxic, oxygen supplementation may be required and those with right heart failure may need diuretics.

Pulmonary Thromboendarterectomy/ Pulmonary Endarterectomy

The treatment of choice for CTEPH is pulmonary endarterectomy (PEA), also called pulmonary thromboendarterectomy

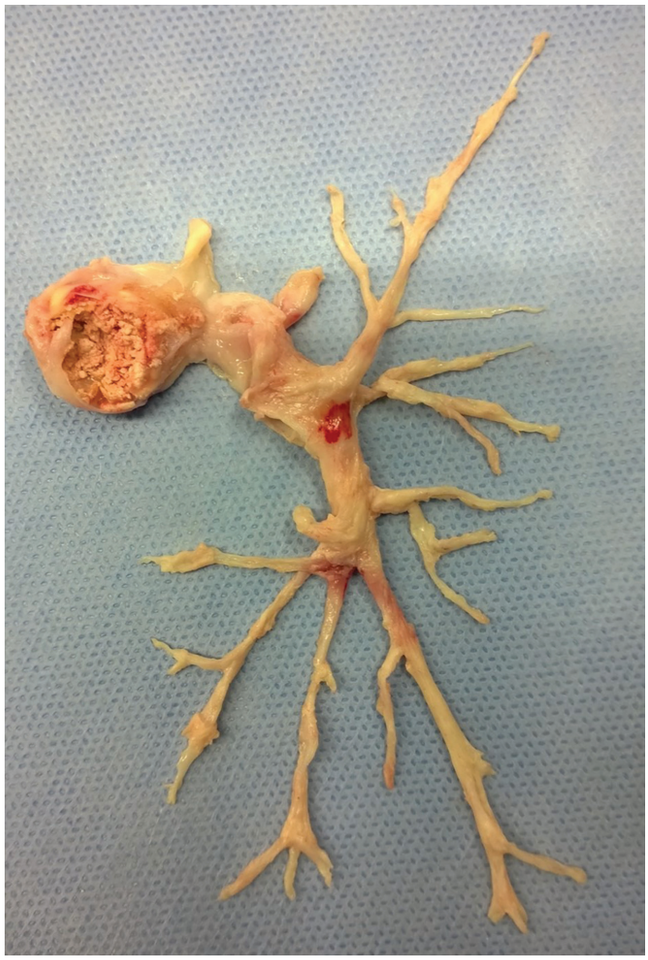

Fig. 15.3 Pulmonary thromboendarterectomy (PTE) specimen showing complete obstruction of the left pulmonary artery with calcification. The fibrous clots extend distally into the subsegmental level but since the disease commences at the level of the left pulmonary artery it is level 1 and as it causes complete obstruction it is level 1C.

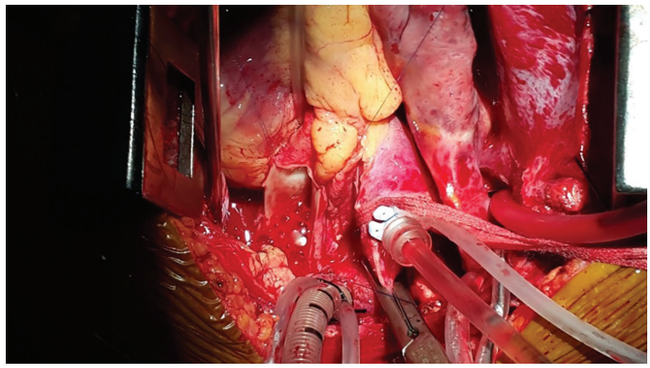

Fig. 15.4 Bubbles seen in the open pulmonary artery on ventilating, indicating a breach of the blood–air barrier during endarterectomy.

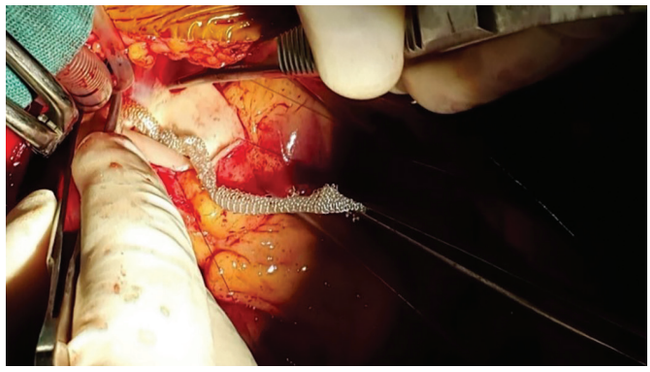

Fig. 15.5 After identifying the subsegmental artery from where air bubbles are coming, a long strip of Surgicel is used to plug the injured vessel.

(PTE). Other treatment modalities are only offered to those who cannot be offered PTE. Data published by an international registry showed a survival advantage for operated patients, with 90% 3-year survival in operated patients compared to 70% in nonoperated patients.[18] The importance of the assessment of operability, preferably by a multidisciplinary team, cannot be overemphasized.

Patients who have severe parenchymal lung diseases such as emphysema or destroyed lungs from previous infections, do not benefit from PTE and that would represent a contraindication. Caution is also advised in patients who have severe left ventricular dysfunction, since the increase in the return to the left artery following PTE may put additional strain on an already dysfunctional left ventricle. Contrary to popular belief, there is no upper limit to the PVR of patients who may be accepted for surgery, but patients with PVR exceeding 12.5 WU may have a higher surgical risk, although the gain from surgery is also high in patients with high PVR.[19] If the patient requires any concomitant cardiac surgery, live coronary artery bypass grafts, or heart valve surgery, they can be combined without much additional risk. Most patients who undergo PTE have severe TR; this need not be addressed in the absence of organic tricuspid valve disease, since the TR will improve once the PAP normalizes.

The operation is usually done through a median sternotomy, though a minimally invasive approach is done in highly selected cases in some very experienced centers, particularly when one is absolutely certain that the disease is entirely unilateral. Cardiopulmonary bypass is established with superior and inferior vena cava cannulas for drainage and ascending aortic cannula for arterial return. The patient is cooled to 18°C in preparation for deep hypothermic total circulatory arrest. The left heart is vented adequately to prevent distention of the left ventricle; authors use vents in the left superior pulmonary vein, pulmonary arteries, and the left ventricular apex. Aortic cross-clamp may be applied, and myocardial protection achieved by a combination of hypothermia and intermittent cardioplegia delivery

as appropriate; alternatively aortic cross-clamp may be avoided with diligent de-airing at the commencement of circulation each time. During this period any concomitant procedures that may be required can be performed. The PEA is performed through incisions in the intrapericardial portions of the left and right branch pulmonary arteries sequentially. This being a bilateral disease, bilateral endarterectomy will be required generally. A critical step in the operation is to identify and raise the correct plane of dissection carefully, the site of which depends on the level of the disease as described earlier. Once the plane is identified, the fibrous clots are held, and the pulmonary artery wall is gently dissected away from the fibrous clot circumferentially. This part of the dissection is done on total circulatory arrest; if the requirement of the arrest period exceeds 20 minutes a period of reperfusion of 10 minutes is done.

The most important step in the operation is to trace all the distal tail ends and remove them completely to remove the obstruction in the pulmonary arteries. Usually, a period of 20 minutes for each side would suffice; sometimes more than one 20-minute period is needed, particularly when the disease is very distal. Once the fibrous clots are removed, the pulmonary artery is filled with saline and the lung is inflated fully, and the artery is inspected for bubbles of air indicating a breach of the blood–air barrier by damage to the pulmonary artery (**Fig. 15.4**). In case such a breach is detected, the injured segmental/sub-segmental branch is identified and plugged[20] with Surgicel (**Fig. 15.5**) or occluded with glue. Several other techniques and algorithms are reported to prevent/manage catastrophic bleeding following PEA. The endarterectomy is always done bilaterally in a sequential manner. After completion of the endarterectomy, the pulmonary artery is closed, and the patient is fully rewarmed and separated from cardiopulmonary bypass.

A continuous cardiac output catheter, pulmonary artery catheter, is floated into the pulmonary artery either in the beginning of the operation or later on. This will give good guidance for the appropriate use of vasoactive medications. The usual drips to start with would be dopamine and noradrenaline, though milrinone has a beneficial effect on the right ventricle and pulmonary vasculature, due to its inodilator effect. If the cardiac index goes up very high, one aims to keep the cardiac index at around 2.5 L/min/m^2. A higher cardiac index may result in reperfusion pulmonary edema. In a hypertrophied right ventricle like the one in CTEPH patients, the coronary blood flow is predominant during diastole, unlike a normal right ventricle where the coronary flow occurs during systole and diastole. Therefore, it is important to maintain adequate diastolic pressure by maintaining adequate systemic vascular resistance (SVR). A low SVR also results in a "steal" from the right coronary artery among other undesirable effects.

Complications

There are some specific complications that may occur following this operation. RV failure following surgery manifests as low PAP and a high central venous pressure and RV contractility can be seen to be low on direct inspection and on transesophageal echocardiography. Appropriate inotropic therapy including use of milrinone may help if the dysfunction is not severe; in severe dysfunction early institution of extracorporeal life support is indicated. Early reperfusion edema may manifest as hypoxia with a low pulmonary flow (PF) ratio. Early initiation of extracorporeal membrane oxygenation (ECMO) would be indicated in this situation as well. Airway bleeding is a very important and life-threatening complication of this operation. This may occur either from a breach in the blood–air barrier from surgical injury to a pulmonary artery branch during endarterectomy or from the systemic to pulmonary collaterals bleeding into the parenchyma. The first thing to be attended to in this situation is to prevent soiling of the contralateral lung. Detection and prevention of airway hemorrhage from surgical injury were described earlier; Kanchi et al[21] have published details of managing airway bleeds of various kinds. Bleeding from collaterals may resolve once the antegrade flow through native pulmonary arteries are re-established. One may need to use ECMO for oxygenation, neutralize the heparin completely, and at times perform embolization of the bleeding collateral with the help of interventional radiologists. The most difficult complication to deal with is persistent pulmonary hypertension. This may be from a mistaken diagnosis of CTEPH; if the pulmonary hypertension was not the result of fibrous clots in the pulmonary arteries, the pressure will not come down by doing endarterectomy, and there may be small vessel disease that is responsible for the high PVR leading to persistent pulmonary hypertension. Inability to obtain adequate surgical clearance may be a rare cause of persistent pulmonary hypertension, particularly in subsegmental disease. ECMO may help to tide over the immediate crisis; further imaging can show if any lesions can be addressed further by interventions and targeted pulmonary vasodilators can also help sometimes. The mortality in this situation is high and transplantation of lungs or heart and lungs with ECMO as bridge to transplant can be done if unable to wean off ECMO. For reperfusion edema venovenous ECMO is used, and for hemorrhage, RV failure, and persistent pulmonary hypertension venoarterial ECMO is used. While on venoarterial ECMO it is important to maintain some antegrade flow in the pulmonary arteries which are now devoid of intima and in the absence of adequate blood flow would form a fresh intraluminal thrombus.

Balloon Pulmonary Angioplasty (BPA)

Though the golden standard for the treatment of this disease is PTE, some patients who are technically inoperable due to very distal disease may benefit from BPA. This has re-emerged with expertise and specific hardware being developed in Japan. In the earlier era the complication rate was unacceptably high but with increasing expertise and better technology, the complication rates are much lower and

might one day replace PTE as the treatment of choice in subsegmental and further distal disease. Currently, the number of centers performing this procedure is low, and it should be restricted to expert CTEPH centers where multimodality treatment facilities are available. A clear correlation is demonstrable between BPA experience and outcomes; also non-BPA interventional experience has not been shown to improve BPA outcomes.[22]

Medical Treatment

All patients following PTE should be on lifelong anticoagulation. Use of targeted pulmonary vasodilators is recommended only in inoperable CTEPH or in those with persistent pulmonary hypertension or recurrent pulmonary hypertension after successful PTE. Some patients with recurrent PH may be eligible for redo-PTE. The approved drug in these situation is Riociguat. Other classes of pulmonary vasodilators have been used off-label for treating CTEPH. In patients who have severe PH and who await surgery or BPA are sometimes treated with pulmonary vasodilators; it may be useful to do so in patients awaiting BPA but the utility of this approach has not been shown to be beneficial in patients undergoing PTE.

Outcomes of Pulmonary Thromboendarterectomy

Successful PEA provides excellent short-term outcomes by improving hemodynamics, exercise capacity, and functional capacity. The in-hospital mortality reported from an experienced center in the most recent 500-patient cohort is 2.2%.[23] A complete follow-up study reported from the UK national series of 880 consecutive patients reported an overall survival of 86% at 1 year, 84% at 3 years, 79% at 5 years, and 72% at 10 years. A mPAP of >30 mm Hg correlated with the need for pulmonary vasodilator therapy postoperatively and a mPAP of >38 mm Hg and PVR of >425 dynes.s^{-1}.cm^{-5} predicted worse long-term survival.[24]

Conclusion

Patients who have had acute pulmonary embolism should be followed up routinely for the development of CTEPH. Though international guidelines do not recommend this, Indian data show a higher number of acute PE patients developing CTEPH than reported elsewhere.[25] A multidisciplinary team should review all the patient data and make the therapeutic choices; the team should determine whether there is pulmonary hypertension, whether the organized, fibrous clots in the pulmonary arteries are the cause for the PH, and what is the best modality of treatment. All operable patients should be offered PTE, and if deemed inoperable, getting a second opinion from an expert CTEPH center would be recommended.

Acknowledgment
We would like to express our heartfelt thanks to Dr. Vimal Raj for providing **Fig. 15.1**.

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