Chronic thromboembolic pulmonary hypertension: a case-based discussion of current management and latest guidelines

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ABSTRACT

Purpose of review: *Frequently underdiagnosed, chronic thromboembolic pulmonary hypertension (CTEPH) is associated with high morbidity and mortality. We highlight recent advancements in evaluation and management.*

Recent findings: *This study focuses on a case-based management approach for CTEPH. It outlines the initial evaluation, treatment approach, and the importance of timely intervention. Although a surgical approach can potentially be curative, we discuss the role of medical management and balloon pulmonary angioplasty (BPA).*

Summary: *This review highlights the importance of early recognition, diagnostic evaluation, and current evidence-based multidisciplinary management of patients with CTEPH.*

Keywords: Chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, balloon pulmonary angioplasty, riociguat.

CASE DISCUSSION

A 71-year-old never-smoker woman with a medical history of asthma, type 2 diabetes mellitus, and obesity presented to the pulmonary clinic 10 days after hospitalization for acute bilateral deep venous thrombosis and intermediate-risk (submassive) bilateral pulmonary embolism (PE). A computed tomography (CT) angiography of the chest showed bilateral pulmonary emboli in the distal left and right main pulmonary arteries. Transthoracic echocardiography (ECHO) showed a dilated right ventricle with decreased function and a D-shaped intraventricular septum. The estimated pulmonary artery systolic pressure (PASP) was 55–60 mmHg. She underwent catheter-directed thrombolysis and was subsequently switched to therapeutic anticoagulation with apixaban (10 mg) twice daily. The only risk factor for venous thromboembolism was chronic use of estrogen replacement therapy for vasomotor symptoms of menopause.

In the clinic, the patient's blood pressure was 118/75 mmHg, heart rate 96/minute, respiratory rate was 18/minute, SpO_2 93% on room air. Physical examination revealed bilateral clear breath sounds, normal heart sounds, trace bilateral pitting pedal edema, and the absence of varicosities. A six-minute walk test (6-MWT) revealed a walking distance of 215.5 m (51% predicted) with oxygen desaturation to the 80s on room air, requiring 2 L/min supplemental oxygen.

Follow-up ECHO revealed persistently elevated PASP levels. Ventilation perfusion (VQ) scans showed multiple large mismatched defects bilaterally. Right heart catheterization (RHC) showed an elevated pulmonary artery pressure (PAP) of 80/30 mmHg (mean, 49 mmHg), pulmonary vascular resistance of 9 Wood units, and elevated pulmonary capillary wedge pressure (PCWP) of 21 mmHg, elevated. [PVR = 49-21/2.9 L/min (Fick cardiac output) = 9 wood units]. These findings suggested combined pre- and post-capillary pulmonary hypertension due to Group IV and Group II etiologies, respectively.

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She was started on furosemide 20 mg orally daily and riociguat 1 mg thrice daily in addition to continuing apixaban 5 mg twice daily for the management of CTEPH. She was referred to the CTEPH Center of Excellence for evaluation of pulmonary thrombendarterectomy (PEA) with a multidisciplinary team comprising specialists in the fields of cardiology, pulmonology, cardiothoracic surgery, and radiology. She underwent PEA 11 months after the initial presentation without perioperative or postoperative complications and was subsequently enrolled in pulmonary rehabilitation.

Three months after PEA, her 6-MWT showed an improvement in walking distance by 58 m. Her resting oxygen saturation improved from 86% to 95% on room air with an improvement in symptoms from WHO class III to WHO class I. An echocardiogram 6 months after PEA demonstrated an improvement in the pulmonary artery systolic pressure to 38 mmHg.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of pulmonary embolism, occurring in 1–5% of acute pulmonary embolism (PE) survivors. It is the only type of pulmonary hypertension (PH) that has a potential cure, namely pulmonary thrombendarterectomy (PEA).[1] According to Gal et al., CTEPH is underdiagnosed and undertreated, with only 16 % of CTEPH cases receiving a diagnosis and only 70% of those diagnosed referred for PEA.[2] Based on national systematic registries, the incidence of CTEPH is between 3.1 and 6.0 patients per million (ppm) with a prevalence from 15.7 to 38.4 ppm. Despite symptoms of dyspnea, exercise limitation, and syncope, there is an average delay in diagnosis of 2 years from the onset of the disease.[3,16] The review highlights CTEPH, a disease with high morbidity and mortality, which without appropriate intervention has a five-year mortality of over 50%, whereas successful PEA results in survival of over 90% at one year and more than 70% at five years.[4]

Pathogenesis of CTEPH

The natural course of PE is the resolution of the clot burden, which results in restoration of the architecture of the pulmonary vasculature, but this takes a different route in patients with CTEPH. Two different factors have been postulated.

Persistent pulmonary arterial obstruction

Persistent narrowing of the pulmonary vasculature due to an organized thrombus can lead to increased pulmonary vascular resistance, vascular remodeling, and pulmonary hypertension. Analysis of the hematological explanation for non-resolution of the thrombus has revealed dysfibrinogenemia, which makes it resistant to plasmin-mediated fibrinolysis. The genetic reasons for this malfunction have not yet been identified.[1,5]

Increased pulmonary blood flow in non-obstructed pulmonary circulation leading to progressive pulmonary vasculopathy

With non-resolution or incomplete resolution of the thrombus in the affected vasculature, redistribution of blood flow through the normal pulmonary arteries causes a new cascade of vascular injury with endothelial dysfunction, smooth muscle hypertrophy, and vascular stress to normal arteries, thereby further elevating pulmonary vascular resistance.[1,5]

Risk factors

Antiphospholipid syndrome (APS) has been associated with CTEPH, with an incidence of 3–7% in CTEPH patients, underscoring the importance of evaluating patients for this condition. Other risk factors for CTEPH include unprovoked PE, treatment delay for PE, chronic inflammatory conditions resulting in hypercoagulability, ventriculoatrial shunt (OR, 76.4), infected pacemaker (OR, 76.4), splenectomy (OR, 17.87), thyroid replacement therapy (OR, 6.1), history of malignancy (OR, 3.76), and non-type O blood groups.[4,17]

Initial evaluation for CTEPH (Table 1)

All patients presenting with significant functional limitations and exercise induced dyspnea occurring after 3 months of anticoagulation following PE should undergo

Table 1. Noteworthy Points[1,5]

ECHO findings with a high probability of PH	Tricuspid valve regurgitation velocity (TRV) > 2.8 m/s (or) TRV < 2.8 m/s + one of the following: • RV End diastolic diameter > 30 mm • Ratio of RVEDD/LVEDD > 0.9 • Hypokinesis of right ventricular free wall • Exertional dyspnea
False positive V/Q scan for CTEPH	Seen in acute PE, venous occlusions, any other conditions causing PA narrowing such as vascular tumors, vasculitis, vascular stenosis.
Diagnostic glitches in CT PA interpretation	Misinterpretation is possible in the absence of a radiologist with a good knowledge of CTEPH. Peripheral artery disease of the pulmonary vasculature is difficult to diagnose.
Newer diagnostics – 3D Lung perfusion MRI	Greater visualization of pulmonary vasculature and perfusion defects.

evaluation for CTEPH. It is important to understand if patients with functional limitation following PE have CTEPH or chronic thromboembolic disease (CTED), which presents with symptoms similar to CTEPH, but without elevated pulmonary artery pressures.

Step 1: Significant functional limitation and exercise-induced dyspnea occurring after 3 months of anticoagulation following acute PE should be evaluated for PH using a screening **Echocardiogram and a 6-MWT**.

Step 2: **Ventilation Perfusion (V/Q) scan** to evaluate patients suspected of having CTEPH in the setting of significant symptoms and positive echocardiographic findings.[5]

Step 3: **CT pulmonary angiography (CT PA)** to identify the anatomical location of the obstructions to evaluate technical operability for PEA. A variation of CT PA, called DECT (Dual energy CT), combines CT and perfusion imaging for anatomical classification and determination of lung perfusion, resulting in 100% sensitivity and specificity for CTEPH.[5]

Step 4: Right heart catheterization (RHC) for accurate diagnosis, with estimation of cardiac output, PAP, PVR, and PCWP combined with a pulmonary angiogram to delineate the anatomy of the pulmonary arteries for PEA or balloon pulmonary angioplasty (BPA).

Management of CTEPH should include the involvement of a multi-disciplinary team, urgent anticoagulation, surgical management of the embolus, medical management of residual pulmonary hypertension, possibility of balloon angioplasty, and long-term supportive care.

Involvement of a multidisciplinary team

The management of CTEPH should involve the expertise of pulmonologists, cardiologists, cardiothoracic surgeons, radiologists, and clinical coordinators to ensure adequate communication within the team.

Anticoagulation

Lifelong anticoagulation is recommended to reduce the risk of recurrent PE in compromised pulmonary vasculature. The choice of anticoagulant (vitamin K antagonists versus direct oral anticoagulants [DOAC]) is very important, particularly in the first 6 months, when the recurrence risk is the highest.[4] Clinicians could consider vitamin K antagonists versus DOAC, i.e.:

Efficacy of anticoagulation: Increased risk of VTE identified with DOAC use (4.42%/person-year) when compared to vitamin K antagonists (0.68%/person-year).[6]

Bleeding risk: No significant difference in major bleeding risk.[6]

Survival: There was no significant difference in pulmonary hemodynamics (PVR) or survival at 48 weeks in the KABUKI trial.[7]

Surgical management with PEA

Pulmonary endarterectomy is a potentially curative treatment option for CTEPH. It is important to evaluate patients for PEA by referring them to a CTEPH center of excellence as soon as the diagnosis is made. Bridging therapy with medical management using Riociguat or BPA before undergoing PEA has not shown a significant benefit and should not delay referral.

Surgical expert centers are those that achieve a mortality rate of <3%, operate on >50 cases / year, have resources for ECMO support if necessary, and have the ability to concurrently perform segmental endarterectomy if needed.[1,5]

Criteria for candidacy

The two most important factors when assessing patients for PEA are the anatomical location of the defects and the expertise of the surgeon. As seen in our patient with distal pulmonary artery disease, successful distal artery PEA has become possible with better surgical expertise and techniques.[8]

Risks and benefits

It is important to be aware not only of the beneficial hemodynamic and functional improvement PEA can provide but also the risks associated with surgery. The only absolute contraindication to surgery is the presence of significant pulmonary parenchymal disease, which may reperfuse after the procedure, resulting in worsening of the V/Q mismatch. Relative contraindications include poor baseline performance status and terminal illness. Pulmonary endarterectomy can normalize PAP in 70–75% of patients[5], with a risk of suboptimal response in patients with WHO functional class IV, right heart failure, and PVR > 15 wood units.

Immediate postoperative complications of PEA

Hypoxia is possible in the immediate postoperative period due to ischemia-reperfusion and redistribution of blood flow from the normal vasculature into endarterectomized segments, causing worsening V/Q mismatch. Reperfusion pulmonary edema can result in severe hypoxemia within 72 hours, which is usually managed conservatively with diuretics, oxygen supplementation, and supportive care. However, inhaled nitric oxide, nebulized prostaglandins, and ECMO support may be required in extreme cases.[5]

Late postoperative complication – residual pulmonary hypertension

The 7th World Symposium of Pulmonary Hypertension has recommended close follow-up of patients undergoing PEA, with imaging and RHC to evaluate for complications, including post-PEA residual PH. Balloon pulmonary angioplasty in addition to medical management has helped improve the WHO functional class and provide symptomatic improvement in this subset of patients.[9]

Those with a mean PAP > 38 mmHg and a PVR > 5.3 wood units in the postoperative period on follow-up 5 years after PEA had worse long-term survival, which emphasizes the importance of long-term follow-up of these patients.[1]

Medical management of pulmonary hypertension

The medical management of CTEPH is used for patients with post-PEA pulmonary hypertension and in patients with contraindications to surgery. Medical management targets the microvasculature of the non-obstructed pulmonary tree, which is adversely affected by the redistribution of blood flow through normal pulmonary arteries.

Choice of medical therapy

Since the 1990s, there has been considerable improvement in the medical management of PAH,

currently with 14 different FDA-approved medications.[3] However, the only FDA-approved first-line medication for the medical management of CTEPH in post-PEA PH and inoperable cases is riociguat, a potent soluble guanylate cyclase (sGC) stimulator.[10]

CHEST-1 was a multicenter, randomized, double-blind, placebo-controlled study demonstrating the efficacy of riociguat, with findings of an improved 6-MWT distance of 54 m and 26 m in inoperable CTEPH and post-PEA residual PH, respectively. This medication also led to significant improvements in WHO functional class, pulmonary vascular resistance, exercise capacity, and survival.[10]

CHEST-2, a follow-up study, was performed to explore the safety profile of riociguat with the 6 MWT and WHO functional class as endpoints. The results of CHEST-1 were sustained for 1 year in CHEST-2, with an adverse effect of hemoptysis/pulmonary hemorrhage occurring in 1.1 patients per 100 patient years.[11]

Multiple medications have been tested but are not approved for CTEPH

The BENEFiT study evaluated the effects of bosentan, an endothelin receptor antagonist, on PVR and the 6 MWT. A significant reduction of PVR of approximately 22% was found in the treatment arm; however, with no change in exercise capacity.[12]

The CTREPH study evaluated the change in 6-MWT and PVR in study groups treated with low or high-dose subcutaneous treprostinil, demonstrating an improvement of approximately 40 m in the high-dose treprostinil arm.[1]

Combination drug therapy for CTEPH

The MERIT-1 study opened doors to combination drug therapy for inoperable CTEPH and post-PEA PH. Macitentan was used in conjunction with a phosphodiesterase inhibitor or an inhaled/oral prostanoid. This study showed an improvement in PVR and 6-MWT at 16 weeks.[13]

Balloon pulmonary angioplasty (BPA)

This is a vascular procedure performed to relieve the obstruction of the pulmonary vasculature in patients with inoperable CTEPH, post-PEA residual PH, and in patients with disease predominantly in the distal arteries. This procedure does not require general anesthesia, and vascular access is obtained through the femoral or internal jugular route, where a balloon is inflated at the site of obstruction to restore the blood flow.[4]

Risks and benefits

The most common adverse events are those occurring during the procedure, such as vascular injury, including pulmonary artery perforation, whereas late complications include those related to the access site, such as pneumothorax and hemothorax.

Advancements in the BPA technique have led to a decrease in adverse outcomes of the procedure. The 30-day post-procedural mortality rate has decreased from 5.6% in 2001 to 2.6% in a multicenter study conducted in Japan between 2004 and 2013.[1] One such advancement is pressure wire-guided percutaneous transluminal pulmonary angioplasty, which results in fewer sessions to attain the desired therapeutic result and fewer complications such as reperfusion pulmonary edema and vascular injury.

The benefits of BPA include an improvement in pulmonary artery pressure and cardiac output, resulting in an improvement in functional class.[14]

Combined therapies

RACE, a multicenter randomized controlled trial, has proven that medical therapy introduced before BPA can improve outcomes. Treatment with riociguat for 6 months in patients with elevated PVR > 4 Wood units resulted in better postprocedural outcomes of BPA.[15]

Supportive Management

As with any other group with PH, patients with CTEPH should be counseled about physical activity,

effective contraception, avoidance of high altitude, supplemental oxygen to prevent hypoxia, diuretics to prevent fluid overload due to cardiac failure in late stages, and appropriate vaccinations.[3]

Directions for future research

More research is needed to identify the risk factors for CTEPH in PE survivors. This would help to develop a structured follow-up plan for high-risk patients to avoid diagnostic delays. It is also imperative to elucidate whether management of acute PE via anticoagulation versus systemic or catheter-directed thrombolysis or thrombectomy has a role in preventing the development of CTEPH.

Combination therapies, including different classes of PH medications and different treatment modalities, including medical, surgical, and vascular procedures, require further study to allow a tailored management approach. Studies comparing inferior vena cava filters to lifelong anticoagulation in patients with CTEPH may provide beneficial results to guide management in patients with a high bleeding risk.

Conclusion

This review discusses a step-by-step approach to the diagnosis and treatment of patients with CTEPH, outlining current practice guidelines based on the best evidence. Although there has been considerable advancement in the understanding of CTEPH, there remain many unanswered questions, challenges, and dilemmas regarding the management of these patients in clinical practice.

Key points

- The only curative treatment for CTEPH is pulmonary endarterectomy.
- The only FDA approved medication for CTEPH is riociguat.
- Lifelong anticoagulation is essential for these patients.

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