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Chronic Thromboembolic Pulmonary Hypertension

Sarfraz Saleemi

Saudi Advisory Group for Pulmonary Hypertension, King Faisal Specialist Hospital and Research Center, Riyadh. Saudi Arabia

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening illness that is often misdiagnosed and underrecognized. It is characterized by a single or recurrent pulmonary thromboemboli that obstruct or obliterate the pulmonary vascular bed as organized tissue, promoting increased pulmonary vascular resistance and progressive pulmonary hypertension and right-heart failure.^[1-4] The involvement of pulmonary microvascular changes in the form of generalized pulmonary hypertensive arteriopathy has been defined relatively recently and is gaining increased recognition as a contributor to disease progression in CTEPH.^[5-7] Many patients with CTEPH present late in the course of disease with progressive dyspnea on exertion, hemoptysis and general clinical deterioration associated with right-heart dysfunction. Nonspecific symptoms and lack of medical history of previous venous thromboembolism (VTE) often complicate accurate diagnosis and, as a result, CTEPH is frequently misdiagnosed and is underrecognized in clinical practice.^[9] Mortality rates without treatment are approximately 70% among patients with a mean pulmonary artery pressure >40 mm Hg, increasing to 90% at >50 mm Hg.^[10] Historically, the occurrence of CTEPH in patients diagnosed with acute pulmonary embolism (PE) has been considered rare. Data from autopsy studies estimated the incidence of CTEPH at 1-3% overall and at 0.1-0.5% in patients surviving acute PE. Every year in the United States, approximately 600 000 individuals suffer an acute pulmonary embolic event and that the annual number of new CTEPH cases in the United States is between 500 and 2500. This may underestimate the true frequency of CTEPH because the disease is often misdiagnosed due to nonspecific symptoms and variable disease course.^[11] A monocenter, prospective, longitudinal study assessing symptomatic CTEPH in patients with acute PE but without prior VTE recently estimated the cumulative incidence of CTEPH to be 1.0% 6 months after PE, 3.1% after 1 year and 3.8% after 2 years and overall post-PE incidence are approximately 3%.^[12] Chronic thromboembolic pulmonary hypertension is often identified during diagnostic work-up in patients with unexplained pulmonary hypertension, many of whom lack medical history suggesting previous VTE. In a recent study of 142 consecutive patients with CTEPH, 90 (63%) had no previous history of symptomatic VTE.^[13]

PATHOGENESIS

The pathogenesis of the disease has not yet been fully

explained and factors contributing to the development of CTEPH remain poorly defined.^[14] The observation that the vast majority of those who suffer an acute PE do not go on to develop CTEPH^[15-16] suggests that there are other factors that are important in the development of the disease. Venous thromboembolism is more common in the elderly, whereas CTEPH often affects younger adults.^[17] Chronic thromboembolic pulmonary hypertension is difficult to replicate through induced PE in experimental studies, and there are striking differences between the organized thrombotic material removed during pulmonary thromboendarterectomy in CTEPH and that retrieved during embolectomy in patients with acute PE. In addition, many conditions that predispose to VTE do not seem to cause CTEPH, suggesting that the two conditions might be unrelated. For instance, markers of congenital thrombophilia are considered as risk factors for VTE but are not prevalent in CTEPH.^[18] No clear link has been established between CTEPH and the occurrence of antithrombin, protein S, protein C or factor II or V Leiden.^[19]

Although organized central thrombi are the most likely disease-initiating event, progressive small pulmonary vessel arteriopathy may contribute to the long-term progression of pulmonary hypertension. Studies also suggest that local (*in situ*) pulmonary thrombosis might contribute to disease progression, promoting the stabilization and growth of thromboemboli.^[20-22]

The current concept of CTEPH pathogenesis is based on gradual formation of organized thromboemboli after deep venous thrombosis and PE. One factor that may be involved in the pathogenic mechanism of the disease is an altered coagulation process, either inherited or acquired, or a combination of both. In addition, a few case reports or small case series have suggested a link between CTEPH and some medical conditions, particularly splenectomy.^[23] Prior splenectomy, ventriculo-atrial shunt, and chronic inflammatory states are independent risk factors for CTEPH.

DIAGNOSIS

V/Q scan

If after history, physical examination, routine investigations and a transthoracic Doppler echocardiogram, a CTEPH is suspected, Ventilation-Perfusion (*V/Q*) lung scan should be ordered. *V/Q* lung scans of patients with CTEPH have generally shown one or more segmental-sized [Figure 1] or larger mismatched perfusion defects.^[24] A normal *V/Q* scan effectively rules out CTEPH.^[25-26] *V/Q* scanning showed sensitivity of 90-100% and specificity of 94-100% in differentiating between idiopathic pulmonary

Address for correspondence: Dr. Sarfraz Saleemi, MBC 46, King Faisal Specialist Hospital and Research Center, P O Box 3354, Riyadh 11211, Saudi Arabia. E-mail: sasaleemi@hotmail.com

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hypertension (IPAH) and CTEPH.^[27] Although negative scan results are highly specific for absence of thromboembolism, false-positive scan results might occur with pulmonary artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.^[28]

Computed tomographic angiography (CTA)

A spectrum of abnormalities on CT scanning have been described in patients with CTEPH including right ventricular enlargement, dilated central pulmonary arteries, chronic thromboembolic material within central pulmonary arteries [Figure 2], increased bronchial artery collateral flow, variability in size and distribution of pulmonary arteries, parenchymal abnormalities consistent with prior infarcts and mosaic attenuation of the pulmonary parenchyma.^[30-32] High-resolution CT (HRCT) of the lung showing a mosaic pattern in CTEPH is virtually diagnostic.^[33] With the advent of multi-slice CT and resolution approaching 0.5 mm in all planes, results for CTA match those obtained with conventional pulmonary angiography.^[34-35]

Magnetic resonance angiography (MRA)

Contrast-enhanced MR angiography (CEMRA) technique can delineate anatomic abnormalities of pulmonary arteries, including the presence of chronic thromboemboli.^[36-37] In one report, the MRI diagnosis of chronic pulmonary thromboembolism matched the V/Q diagnosis in 92% of cases.^[38] Contrast-enhanced, 3D magnetic resonance angiography may permit the detection of central chronic thromboembolic material and might be equivalent to digital angiography to the level of segmental arteries.^[39] Surgical intervention is largely limited to proximal and segmental vessels and in a study by Kreitner and colleagues, CEMRA correctly predicted surgical success in 33 of 34 patients.^[40]

Doppler echocardiography

Doppler echocardiography can provide information that may help differentiate between CTEPH and IPAH. In a retrospective, unblinded study of 35 patients known to have either CTEPH (19 patients) or IPAH (16 patients), Doppler echocardiography-derived pulmonary pulse pressure normalized by sPAP or mPAP separated these two groups with a sensitivity of 0.95

and specificity of 1.00. Cutoff values have been 0.77 and 1.35 for pulse/systolic pressure and for pulse/mean pressure, respectively.^[41]

Pulmonary angiography

At present, pulmonary angiography remains the diagnostic procedure of choice for the evaluation of suspected CTEPH. By identifying occlusions and intravascular webs, it confirms the diagnosis and gives an indication of operability.^[42-44]

Pulmonary angiography

Pulmonary angiography is invasive and expensive and carries a small but definite risk. Although it has been shown that angiography can predict hemodynamic outcome in patients with relatively mild PH and can confirm operability in patients with severe PH, noninvasive methods providing similar information are increasingly becoming available.^[45]

MANAGEMENT

Pulmonary endarterectomy

All patients with CTEPH should be evaluated for pulmonary endarterectomy (PEA) as first line treatment since it is potentially curative.^[46-48] CTEPH with thromboembolic defects at main, lobar or proximal segmental level are characterized as possessing proximal disease and represent the main cases for operability.^[49-50] Patients with significant PH but with little or no visible evidence of thromboembolic pathology are considered poor candidates for surgery.^[50-51]

Factors which favor the decision to perform PEA are [Figure 3]:

- Proximal accessible lesions*
 - Patient consent*
 - Absence of major comorbidity*
 - mPAP >40 mm Hg*
 - PVR > 300 dyn s/cm⁵*
 - NYHA Class III/IV*
 - Surgical expertise*
- (mPAP- mean pulmonary artery pressure, PVR-Pulmonary

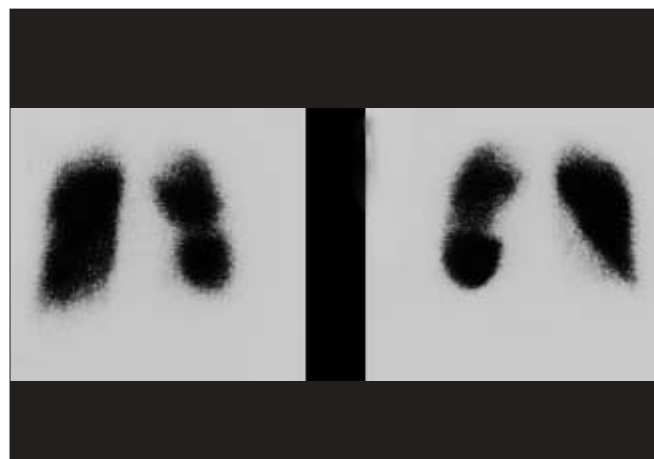


Figure 1: Perfusion lung scan in a patient with CTEPH showing multiple segmental defects

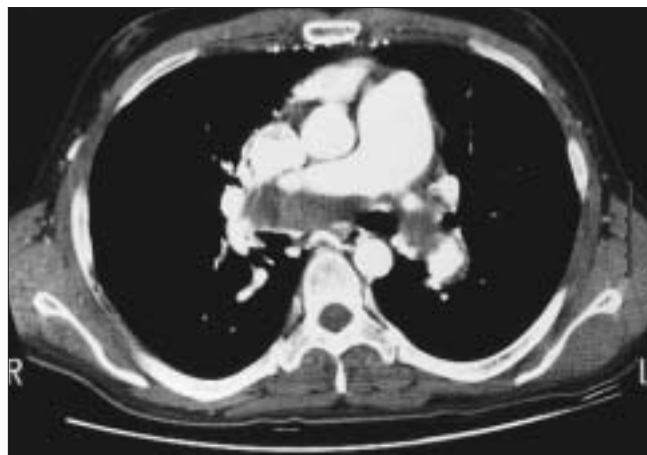


Figure 2: Computed tomographic angiogram in a patient with CTEPH showing partially organized thrombus lining both right and left pulmonary arteries, with narrowing of the right main pulmonary artery at the origin of the upper lobe. Asymmetric wall thickening is also evident along the lateral aspect of the left descending pulmonary artery. (With permission from LEWIS J. RUBIN)

vascular resistance, NYHA- Newyork Heart Association)

Currently, advanced age, concomitant cardiac disease (e.g. coronary artery disease), severe right ventricular failure, renal or hepatic insufficiency and malignancy with reasonable survival expectations are not considered absolute contraindications. However, patients with severe left ventricular dysfunction or significant obstructive or restrictive lung disease are not accepted for surgery. Patients with suprasystemic pulmonary artery pressures and excessive elevation of pulmonary vascular resistance ($>1500 \text{ dyne.s/cm}^5$) are considered significantly high-operative risk.^[52] The goals of the operation are restoration of lung and ventilation perfusion balance, reduction of right ventricular afterload and avoidance of a secondary vasculopathy in patent pulmonary arteries [Figure 4]. Basic essentials of postoperative care are: maintenance of adequate right ventricular function, organ perfusion, renal function, sufficient oxygenation and prevention of early pulmonary artery reocclusion.^[53]

Balloon angioplasty

Balloon pulmonary angioplasty (BPA) is a possible option in patients with CTEPH deemed inoperable for PEA or with significant residual postoperative PH. In a nonrandomized trial, BPA reduced pulmonary artery hypertension in patients with CTEPH and are associated with long-term improvement in New York Heart Association class and 6-min walking distances.^[54] Balloon pulmonary angioplasty is a promising interventional technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgical candidates.

Lung transplantation

Lung transplant (LT) or Lung heart transplant (LHT) might also be a viable option for some patients with inoperable CTEPH or postoperative persistent pulmonary hypertension.

Medical therapy

A substantial proportion of patients with CTEPH are considered inoperable. Prognosis in the absence of surgery is very poor, particularly in those with a mean pulmonary artery pressure (mPAP) $>50 \text{ mm Hg}$, with 5-year survival rates as low as 10% in the most severely affected patients.^[55-58] Targeted medical

therapy is found to be useful in treating patients who are poor candidates for surgery and in post-PEA persistent pulmonary hypertension. During initial studies, prostanoids both IV and inhaled, the dual endothelin receptor antagonist Bosentan and the PDE-5 inhibitor sildenafil have all shown potential in the treatment of inoperable CTEPH.^[59-68] Many experts also agree that combinations of prostanoids, endothelin receptor antagonists and PDE-5 inhibitors will play a major role in therapy in the future.^[69-70] Results from first ever randomized trial, BENEFIT, on use of Bosentan in CTEPH showed significant hemodynamic benefit in term of decrease in pulmonary vascular resistance and improved cardiac index although there are no significant increase in 6-min walk distance [Figure 5].^[71]

CONCLUSION

Chronic thromboembolic pulmonary hypertension should be considered in any patient with unexplained pulmonary hypertension. V/Q lung scan should be ordered as an initial investigation if CTEPH is suspected. CTA and/or MRA should be considered to assess pulmonary vasculature and parenchyma. Patients considered suitable for PEA should be referred to a higher center with expertise in this field. Pulmonary angiogram should be performed before PEA to plan a surgical road map. PEA should be considered as the first treatment option, where possible. Current basic criteria for the application of PEA include NYHA functional Class III or IV symptoms, a preoperative pulmonary vascular resistance of $>300 \text{ dyne.s/cm}^5$, surgically accessible thrombus in the main lobar or segmental pulmonary arteries and no severe comorbidities. Pulmonary hypertension is likely to persist after PEA in patients with significant pulmonary arteriopathy, resulting in poor clinical outcome and increased perioperative mortality. In patients not eligible for PEA due to the presence of collateral and/or surgically inaccessible lesions, balloon angioplasty has been suggested as a possible alternative at some centers; however, it is considered experimental and requires further assessment. In the absence of severe comorbidity, lung transplantation may provide a further option in cases where PEA has failed. Medical therapy has shown potential in uncontrolled and observational studies. Results from recently published randomized controlled trial, BENEFIT, in which

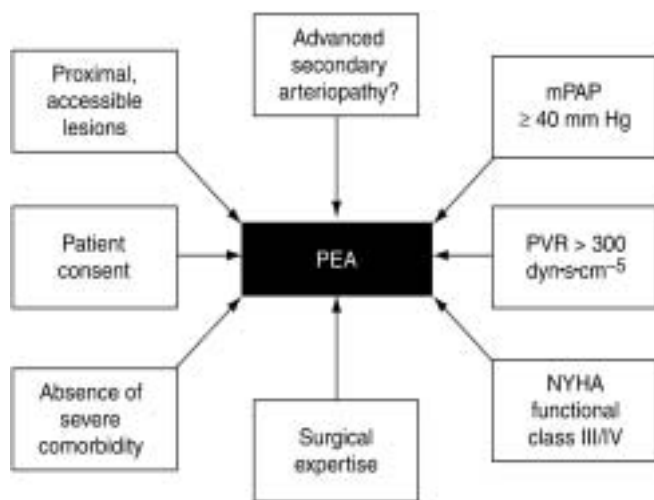


Figure 3: Factors considered in assessments of operability for pulmonary endarterectomy (Adapted with permission from Proc Am Thorac Soc Vol 3. pp 601–607, 2006)

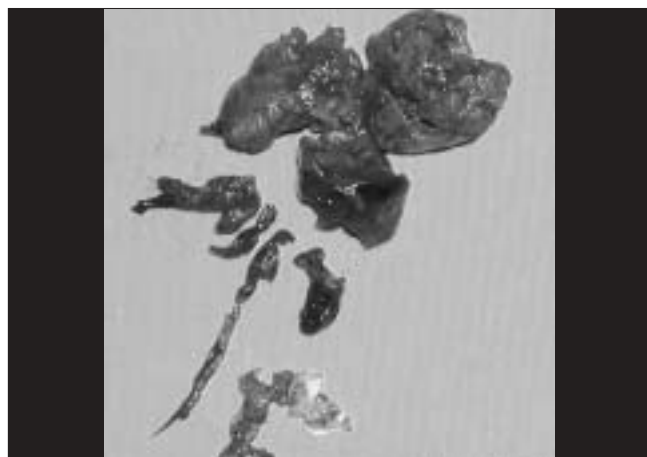


Figure 4: Example of material obtained during pulmonary endarterectomy procedure

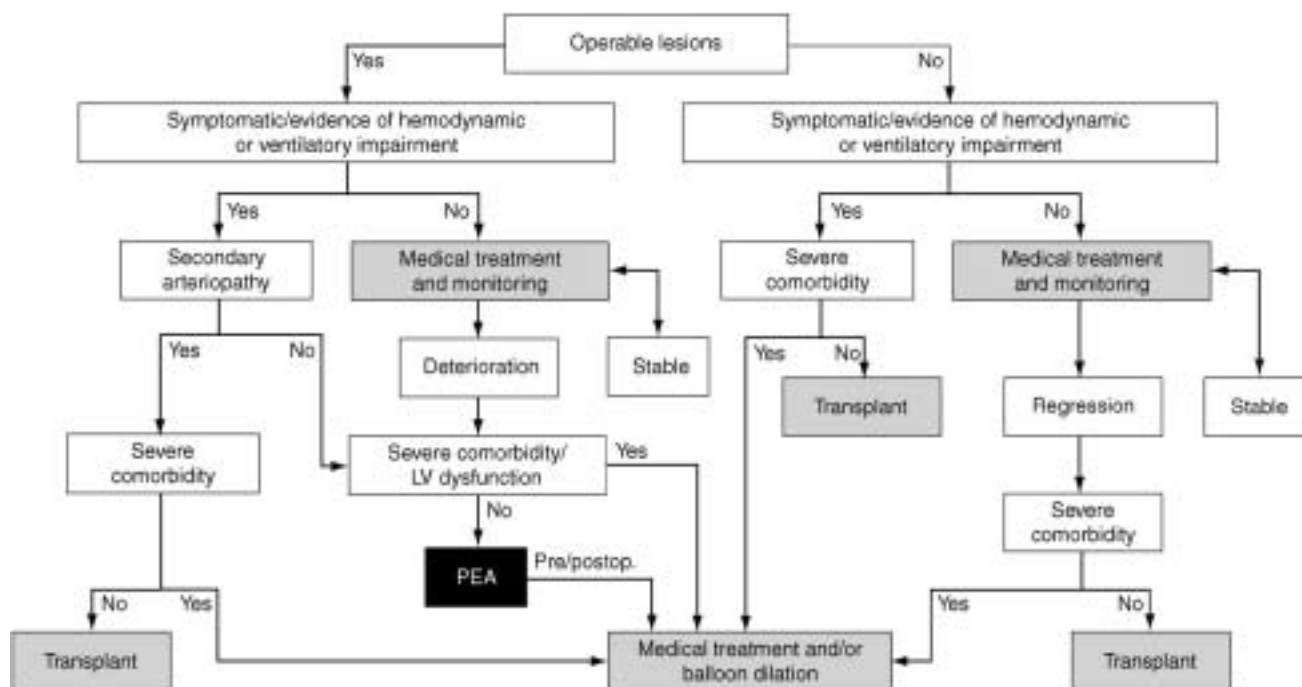


Figure 5: Algorithm for management of CTEPH (Adapted with permission from Proc Am Thorac Soc Vol 3. pp 601–607, 2006)

Bosentan are used in patients with CTEPH, appear promising in terms of hemodynamic benefit although it did not translate into improvement in 6-min walk distance.

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