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Case Report

Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH): Case Presentation and Guidance on Management

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Abstract

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is defined as an elevation of the mean pulmonary arterial pressure above 25 mmHg that persists six months after an episode of pulmonary embolism (PE). It occurs an about 2 - 4% in survivors from PE. The clinical picture, natural history and prognosis may vary from one patient to another.

Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and PE is the third most common cardiovascular illness after acute coronary syndrome and stroke.

A 29 year old male patient presented with gradually progressive shortness of breath and fatigue for several months. He had one episode of loss of consciousness. Clinical examination revealed picture of pulmonary hypertension. Further laboratory and imaging confirmed the presence of recent pulmonary embolism and markedly elevated pulmonary arterial pressure, consistent with the diagnosis of CTEPH.

In this article, we discussed this clinical case, the diagnostic pathway and the management plan that was followed with the patient till his last follow-up, focusing on guidance on management in the same context.

We believe that addressing VTE as a possible regional public health problem should take a multi-dimensional approach targeting the epidemiology of the disease with implementation of cost-effective preventive and therapeutic programs.

Keywords: *Chronic Thrombo-Embolic Pulmonary Hypertension; Venous Thrombo-Embolism; Deep Vein Thrombosis; Pulmonary Embolism; Congenital Thrombophilia; Anticoagulants*

Introduction

Venous thrombo-embolism (VTE),comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) is known to be a common reason of mortality and morbidity among hospitalized and bedridden patients, and also among healthy individuals. After acute coronary syndrome and stroke, VTE is considered the third most prevalent cardiovascular disorder [1]. PE has been considered the third most common and most preventable source of hospital-related deaths [2-4].

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is one of the life threatening complications of PE and it can progress to right-heart failure [5]. Without intervention, CTEPH has poor survival [6].

Here we report the case of a young male patient who suffered from recurrent pulmonary thrombo-embolic events which resulted in CTEPH. We review the literature and provide guidance on management.

Case Report

A 29 year old Pakistani male driver, presented with breathing difficulty on exertion of one year duration. He had a history of progressive breathing difficulty increasing from NYHA I to NYHA III with occasional difficulty at rest (NYHA IV) accompanied by sweating and an episode of loss of consciousness one week before presentation. He had no significant past medical, surgical or family history of note. There was a history of tobacco chewing for long time and last history of travel was 9 months earlier. On clinical examination, his vital signs showed a blood pressure of 130/80 mmHg, a regular pulse rate of 103 beats per minute, a respiratory rate of 22/min, and an Oxygen saturation of 98% on room air. His jugular venous pressure was elevated up to the mastoids with prominent "a" and "v" waves. There was no central cyanosis, no pallor or clinical jaundice. Local cardiovascular examination revealed local signs of pulmonary hypertension and right ventricular hypertrophy. He was admitted for further management.

Initial work up revealed: elevated D-Dimer levels, normal serum cardiac Troponin, normal liver function tests, renal function tests and coagulation profile. His 12 leads surface electrocardiogram (ECG) revealed resting sinus tachycardia, right atrial abnormality, right ventricular hypertrophy with strain pattern and right axis deviation (Figure 1). Chest X-Ray showed prominent pulmonary artery, evidence of pulmonary oligemia, bilateral pleural effusion and other signs of pulmonary hypertension (Figure 2). Echocardiography revealed picture of cor-pulmonale with dilated right atrium and right ventricle, severe tricuspid valve incompetence, and severe pulmonary hypertension with an estimated systolic pulmonary arterial pressure of 90.0 mmHg (Figures 3a, 3b). CT pulmonary angiography revealed multiple hypodense filling defects bilaterally impressive of recent pulmonary artery thromboembolism (Figures 4a, 4b).

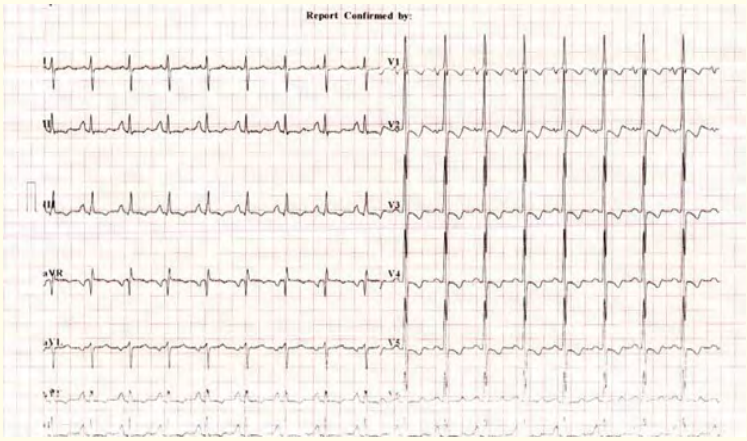

Figure 1: *ECG of the patient showing: sinus tachycardia, right atrial abnormality, right ventricular hypertrophy with strain pattern and right axis deviation.*

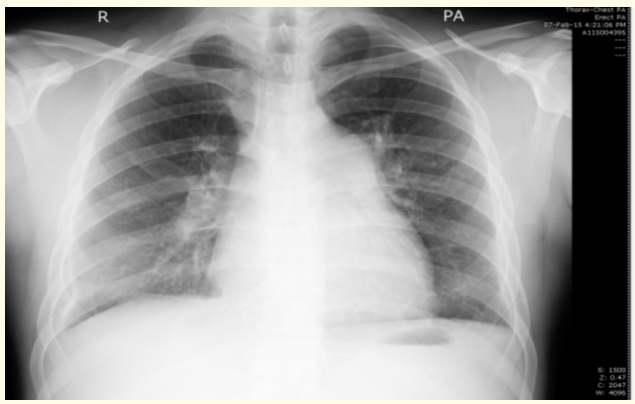

Figure 2: *Chest X-ray: Prominent pulmonary artery, evidence of pulmonary oligemia, bilateral pleural effusion and other signs of pulmonary hypertension*

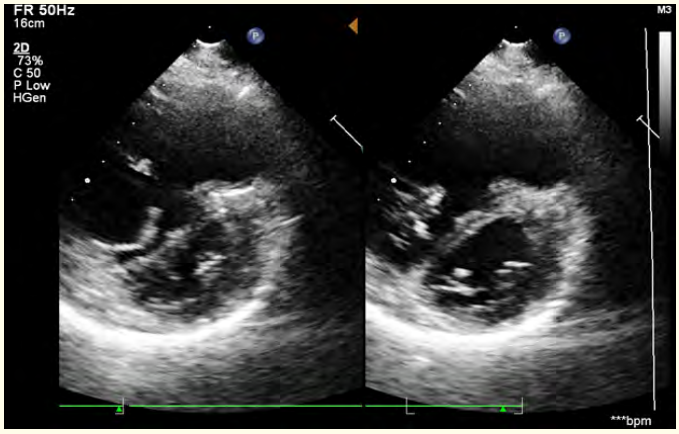

Figure 3a: *Transthoracic echocardiography showing D-shaped interventricular septum in systole and diastole, which are signs of right ventricular pressure overload and volume overload.*

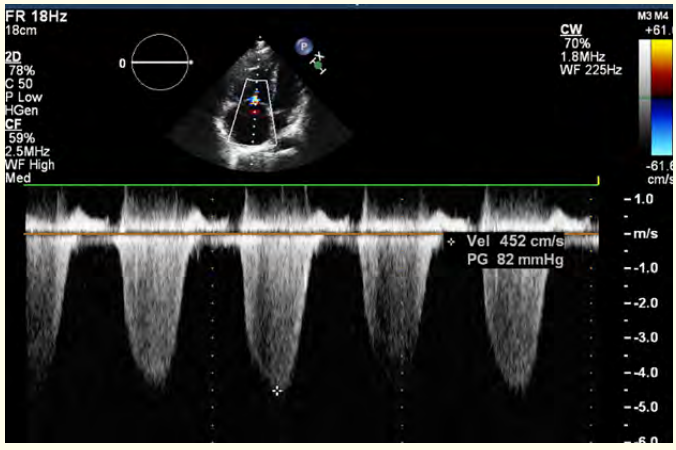

Figure 3b: *Continuous wave Doppler tracing across the jet of tricuspid valve regurgitation. The estimated systolic PAP can be derived to be around 95.0-100.0 mmHg.*

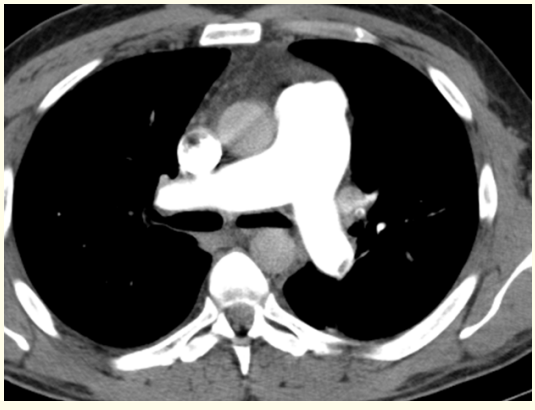

Figure 4a: *CT pulmonary angiography showing multiple hypodense filling defects bilaterally suggestive of recent pulmonary artery thromboembolism.*

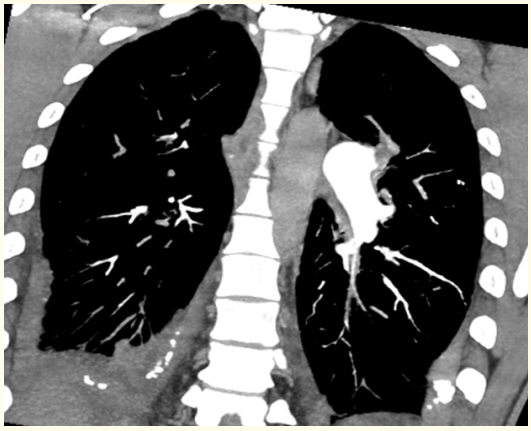

Figure 4b: *CT pulmonary angiography showing bilateral pleural effusion in addition to multiple hypodense filling defects bilaterally.*

A diagnosis of recurrent pulmonary emboli complicated by chronic thrombo-embolic pulmonary hypertension (CTEPH) was made. He was kept on low-molecular Heparin treatment during hospitalization and discharged on oral anticoagulant therapy (Rivaroxaban) 15 mg twice daily (for a total of 21 days) then 20 mg once daily as a maintenance dose and titrated doses of Diltiazem till 90 mg twice daily was reached. He was advised about thrombophilia screening, surgery review and close follow-up. On next follow up in the two weeks later, he had felt clinically better.

One month later, he was referred from the airport before travelling as he had developed syncope in the airport. On examination he was restless, tachypneic, tachycardic and had generalized body swelling, icterus, ascites, hepatomegaly and bilateral lower limb edema. He was admitted for liver cell dysfunction as a result of right sided heart failure as he was found to have deranged liver function tests, with slightly increased homocysteine level. He was managed medically and his condition gradually improved and discharged after a few days but was lost to follow-up later.

Discussion

CTEPH was first recognized in the 1940s at post mortem, and first reported in the UK in 1951 [7].

Pulmonary hypertension (PH) is defined as the mean pulmonary arterial pressure (MPAP) of greater than 25 mmHg at rest, where normal values of MPAP is less than 20 mmHg, systolic PAP: 15 - 30 mmHg and diastolic PAP: 4 - 12 mmHg) [8].

PH has been classified as: Group 1Pulmonary Arterial Hypertension, Group 2PH due to left heart disease, Group 3- PH due to chronic lung disease and/or hypoxemia, Group 4 Chronic Thromboembolic Pulmonary Hypertension (CTEPH), Group 5- PH with unclear or multifactorial etiologies [9].

CTEPH is defined as pulmonary hypertension (more than 25 mmHg) that persists 6 months after PE [10]. It occurs in 2 - 4% after PE [11].

The diagnostic criteria for CTEPH include (i) presence of pulmonary hypertension(MPAP ≥ 25 mmHg) at rest in the absence of elevated pulmonary capillary wedge pressure (PCWP ≤ 15 mmHg), (ii) Thromboembolic occlusion of the proximal or distal pulmonary vasculature that is presumed to be the cause of PH [12].

Epidemiologically, It has been found that 1 to 2 per 1,000 people get affected by VTE every year [13]. Nearly one among 20 people develops DVT during their lifetime [14]. Each year, in the United States, about 600,000 persons have an acute PE [14].

The prevalence and incidence of CTEPH have been grossly underestimated. It is estimated that there are between 500 and 2500 new cases of CTEPH diagnosed each year [14]. Once considered a rare condition, CTEPH has been recently documented to complicate 3.8% of acute pulmonary embolic events [15]. In previously treated PE patients (with at least three months of oral anticoagulation), 1 out of every 25 develop CTEPH [14].

A single or recurrent pulmonary emboli arising from venous thrombosis sites can result in CTEPH [6]. According to the "embolic hypothesis," these PE lead to endothelialized residua that obstruct or significantly narrow pulmonary arteries [16].

According to Kim., *et al*. PE-related risk factors include recurrent or unprovoked PE, large perfusion defects, young age at detection of PE, a systolic pulmonary arterial pressure greater than 50mmHg, and persistent PH on echocardiography performed 6 months after acute PE [17]. Furthermore, treatment for PE does not rule out the possibility of development of CTEPH.

In addition to these PE-related risk factors, some medical conditions independent of PE have been associated with increased risk of CTEPH. These include infected surgical cardiac shunts or pacemaker or defibrillator leads, splenectomy, chronic inflammatory disorders, thyroid replacement therapy and malignancy.

Interactions between genetic, acquired, and circumstantial risk factors resulting in VTE, can lead to CTEPH. Thrombotic factors include lupus anticoagulant or antiphospholipid antibodies, increased factor VIII levels, dysfibrinogenemia and genetic factors like ABO blood groups other than O, HLA polymorphisms, and abnormal endogenous fibrinolysis [18-20].

CTEPH is underdiagnosed most of the time, often misdiagnosed as another disease. Patients with CTEPH may or may not have a history of PE. The symptoms are nonspecific; therefore it is indistinguishable from other causes of severe PH [5]. The common symptoms include progressive dyspnea on exertion, rapid exhaustion, and fatigue. However, it is important to distinguish CTEPH from PAH and other types of pulmonary hypertension, because CTEPH is the only potentially curable form of pulmonary hypertension [5].

In the majority of patients, months or even years may pass between an event of acute PE and manifestation of clinical signs of CTEPH "honeymoon period" [5]. Signs of right-heart failure occur later in the course of the disease [5].

ECG may show signs of right ventricle overload (commonly: negative T waves in precordial V1-V5 leads, negative T wave in II, III, aVF, pulmonary P wave and right axis deviation) [21].

Echocardiography is useful in the initial assessment of suspected PH [22]. An echocardiogram may be performed 6 weeks after acute PE to screen for persistent PH which may predict the development of CTEPH [23].

A ventilation/perfusion (V/Q) lung scan is performed early in the diagnostic pathway to differentiate patients with CTEPH from those with other forms of pulmonary hypertension. In CTEPH, the V/Q scan is almost always assessed as "high probability" with multiple mismatched segmental perfusion defects evident. A normal or low probability scan effectively rules out the diagnosis of CTEPH. V/Q scan is the preferred and recommended screening test for CTEPH [17].

Following the initial diagnosis of CTEPH, subsequent investigations aim to define the nature and extent of thrombo-embolic disease and thus assess surgical suitability. Pulmonary angiography (digital subtraction angiography) remains the gold standard for confirmation of CTEPH and evaluation of operability [17]. More recently; magnetic resonance (pulmonary) angiography and computed tomographic pulmonary angiography (CTPA) have been used for this purpose. Right heart catheterization is used for hemodynamic evaluation to confirm the presence of PH and to provide prognostic information [22].

Other investigations include pulmonary function tests which can assess the functional capacity of the lungs, thrombophilia screening and evaluation of Collagen diseases [22].

Possible differential diagnoses include valvular lesions (aortic/mitral/pulmonic), cardiomyopathies, coronary artery disease, pulmonary vascular disease and chronic lung disease (asthma/COPD).

Radiologically conditions mimicking CTEPH include pulmonary artery sarcoma, fibrosing mediastinitis, and large vessel arteritis (Takayasu disease). It is important to recognize these conditions as they are not amenable to PEA, although pulmonary artery sarcoma can be effectively palliated with surgical resection in some cases. The distinction between these conditions and CTEPH on diagnostic imaging is often subtle, further highlighting the need for these patients to be seen at centers with experience in assessing such patients.

Standard therapy for pulmonary hypertension (PH) involves adequate hydration and nutrition, early treatment of infections, treatment of underlying cause, long-term oxygen therapy, treatment of heart failure, therapeutic anticoagulation, PAH-specific therapy and surgery.

In the management of CTEPH patients, the first step is to initiate anticoagulant therapy. These patients should receive life-long anticoagulation, usually with vitamin K antagonists adjusted to a target INR between 2.0 and 3.0 [25]. Anticoagulants include unfractionated Heparin/ low-molecular weight Heparin (UFH/LMWH), Warfarin or the recently approved novel oral anticoagulants (NOACs), like: Rivaroxaban, Dabigatran, and Apixaban.

The next step in CTEPH management is evaluation of these patients for pulmonary thromboendarterectomy (PEA). Surgery is the only definitive therapy for CTEPH and PEA is the surgical procedure of choice. It is regarded as the only potentially curative therapy, apart from a lung transplant. Prior to proceeding with PEA, a three-month period of anticoagulation is required. A CTEPH team, consisting of an experienced PEA surgeon and CTEPH physicians, should assess operability for PEA surgery. Close working collaboration between community providers and CTEPH centers is required [17,22]. The decision to proceed to pulmonary thromboendarterectomy is based upon four criteria: the surgical accessibility of the thrombi; the presence of hemodynamic and/or ventilatory impairment; the impact of the patient's comorbidities on the risks of the surgery; and the willingness and motivation of the patient to undergo surgery [26]. After an effective intervention, a dramatic drop of pulmonary vascular resistance is expected with a near normalization of pulmonary haemodynamics [26].

A new surgical technique called balloon pulmonary angioplasty may also offer an alternative treatment for inoperable CTEPH patients. Although it requires further investigation, it is rapidly gaining attention because in the elderly and frail, high-risk cure may be less desirable than low-risk palliation [27]. BPA has been refined in Japan to be established more widely.

Other surgical therapies include Double-lung transplantation which is an alternative surgical option for selected cases where PEA is not indicated, or when significant pulmonary hypertension persists following PEA [28].

Medical therapy is considered the final step in the management of CTEPH patients. Medical therapy for CTEPH refers to the use of pulmonary vasodilators and remodeling agents to lower the pulmonary vascular resistance and pulmonary artery pressure, thereby improving symptoms and signs such as exercise capacity and oxygenation. It should only be administered at specialized centers that have experience treating patients with pulmonary hypertension. Medical therapy is not curative and its effects are relatively modest; therefore, it is indicated in only a few clinical situations: (i) patients who are not operative candidates; (ii) patients who have a suboptimal hemodynamic and functional outcome following PEA (persistent CTEPH); and (iii) as a bridge to definitive surgical intervention in patients with severe pulmonary hypertension and right heart failure [26,29].

Medications used to treat CTEPH are those that are used to treat idiopathic pulmonary arterial hypertension. They include drugs in the following classes: 1) Prostanoids (Prostacyclin pathway agonists) like Epoprostenol, Treprostinil, and Iloprost, 2) Endothelin receptor antagonists (Bosentan, Ambrisentan, Macitentan), 3) Nitric oxide-cyclic guanosine monophosphate enhancers including soluble Guanylate Cyclase stimulants (Riociguat) and Phosphodiesterase 5 inhibitors (Sildenafil, Tadalafil, Vardenafil) [30]. Riociguatis the first approved medical treatment demonstrating efficacy in this condition [31,32].

The agent selection is generally based upon factors including patient preference, cost, availability, safety, route of administration, and functional class (World Health Organization [WHO] [33] or New York Heart Association [NYHA] [34].

Studies have found that for inoperable CTEPH, (i) ERA particularly Bosentan has been beneficial for patients with WHO functional class II to IV; mild to severe [35], (ii) soluble Guanylate Cyclase stimulant, Riociguat is the preferred agent for patients with functional class II to III [36], (iii) Phosphodiesterase 5 inhibitors (oral Sildenafil) for functional class II to III [37], (iv) Prostanoids for functional class IV patients [38].

In patients who have persistent CTEPH post PEA, oral Riociguat may be the preferred agent, particularly in those with functional class II or III disease. However, for severely ill functional class IV patients, Prostanoids may be preferred [32].

In patients with severe life-threatening CTEPH (e.g. patients with hemodynamic indices of severe pulmonary hypertension and symptoms of severe right heart failure), medical therapy is used as a therapeutic bridge to help patients survive to definitive pulmonary thromboendarterectomy [39,40]. However, it should not be routinely used as a preoperative therapy and in particular, should not delay appropriate referral for pulmonary thromboendarterectomy.

In terms of severity, for patients who are not severely ill (i.e. NYHA or WHO functional Class II or III), the preferred agents are Riociguat, Bosentan or Dildenafil. For patients who are severely ill (i.e. NYHA or WHO functional Class IV), the preferred agent is a Prostanoid (intravenous epoprostenol or treprostinil) [41].

All patients diagnosed with CTEPH should receive lifelong anticoagulation. Up to one-third of patients may have residual CTEPH following pulmonary thromboendarterectomy [17]. Consider reassessing PAH patients who have not received a V/Q scan to see if they have potentially operable, potentially curable CTEPH.A V/Q scan is an important diagnostic test for patients with suspected PH or PE patients who are still symptomatic after 3 months of anticoagulation [17].

Pulmonary hypertension (PH) is progressive, and fatal, if untreated. Survival is usually 2 - 3 years from the time of diagnosis. The prognosis of PH is highly variable and depends upon the type and severity of the disease. The causes of death include right ventricular failure, sudden cardiac death, recurrent PE, and perioperative complications.

In patients with CTEPH who received no intervention, the 5-year survival rate was 30% with mean pulmonary artery pressure (mPAP) > 40 mmHg and 10% with mPAP > 50 mmHg [6]. Perioperative mortality among patients undergoing pulmonary thromboendarterectomy has decreased. Mortality due to CTEPH is low among patients who survive three months post-thromboendarterectomy [42]. Less than 0.5 percent of all patients who have undergone a pulmonary thromboendarterectomy develop recurrent thromboembolic disease that requires a repeat pulmonary thromboendarterectomy [43].

Conclusion

CTEPH is an important cause of severe pulmonary hypertension, which has been under recognized in the past. Appropriate diagnosis and assessment is vital as the majority of patients with this condition can be effectively cured with pulmonary endarterectomy.

For those patients unsuitable for surgery, or with significant pulmonary hypertension post-PEA, PAH specific drugs may be an effective therapeutic option. However, there is still a need for more trials targeting (i) patients who need to be bridged to pulmonary thromboendarterectomy/intervention because available data are uncontrolled and restricted to PEA;(ii) patients who are technically inoperable; (iii) patients who are technically operable but have an unacceptable surgical risk; and (iv) patients with symptomatic residual/recurrent PH after PEA.

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Bibliography

1. "2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC), Endorsed by the European Respiratory Society (ERS)". *European Heart Journal* (2014): 5.

2. Gjonbrataj E., *et al*. "Risk factors associated with provoked pulmonary embolism". *The Korean Journal of Internal Medicine* 32.1 (2017): 95-101.

3. Kerkez, *et al*. "A study of pulmonary embolism after abdominal surgery in patients undergoing prophylaxis". *World Journal of Gastroenterology* 15.3 (2009): 344-348.

4. Asuka Ozaki and John R Bartholomew. "Venous Thromboembolism (Deep Venous Thrombosis & Pulmonary Embolism)".

5. Jennifer Haythe. "Chronic thromboembolic pulmonary hypertension: A review of current practice". 55.2 (2012): 134-143.

6. Fedullo P., *et al*. "Chronic Thromboembolic Pulmonary Hypertension". *American Journal of Respiratory and Critical Care Medicine* 183.12 (2011): 1605-1613.

7. William., *et al*. "Chronic Thromboembolic Pulmonary Hypertension. The Journey from a Curiosity to a Cure". *Annals of the American Thoracic Society* 13.3 (2016): S197-S200.

8. Marius M Hoepe., *et al*. "Definitions and Diagnosis of Pulmonary Hypertension". *Journal of the American College of Cardiology* 62.25 (2013): D42-D50.

9. Gerald Simonnea., *et al*. "Updated Clinical Classification of Pulmonary Hypertension". *Journal of the American College of Cardiology* 62.25 (2013): D34-D41.

10. Gerald Simonnea., *et al*. "Updated Clinical Classification of Pulmonary Hypertension". *Journal of the American College of Cardiology* 54.1 (2009): S43-S54.

11. Becattini C., *et al*. "Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism". *Chest* 130.1 (2006): 172-175.

12. Wilkens H., *et al*. "Chronic thromboembolic pulmonary hypertension (CTEPH): Updated Recommendations of the Cologne Consensus Conference 2011". *International Journal of Cardiology* 154.1 (2011): S54-S60.

13. Beckman MG., *et al*. "Venous thromboembolism: a public health concern". *American Journal of Preventive Medicine* 38.4 (2010): S495-S501.

14. Tapson V., *et al*. "Incidence and prevalence of CTEPH: from acute to chronic pulmonary embolism". *Proceedings of the American Thoracic Society* 3.7 (2006): 564-567.

15. Pengo V., *et al*. "Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism". *The New England Journal of Medicine* 350.22 (2004): 2257-2264.

16. Humbert M. "Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology". *European Respiratory Review* 19.115 (2010): 59-63.

17. Kim NH and Lang IM. "Risk factors for chronic thromboembolic pulmonary hypertension". *European Respiratory Review* 21.123 (2012): 27-31.

18. Bonderman D., *et al*. "Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension". *Thrombosis and Haemostasis* 93.3 (2005): 512-516.

19. Blauwet LA., *et al*. "Surgical pathology of pulmonary thromboendarterectomy: a study of 54 cases from 1990 to 2001". *Human Pathology* 34.12 (2003): 1290-1298.

20. Bernard J and Yi ES. "Pulmonary thromboendarterectomy: a clinicopathologic study of 200 consecutives pulmonary thromboendarterectomy cases in one institution". *Human Pathology* 38.6 (2007): 871-877.

21. Lewczuk., *et al*. "Electrocardiographic signs of right ventricular overload in patients who underwent pulmonary embolism event(s). Are they useful in diagnosis of chronic thromboembolic pulmonary hypertension?" *Journal of Electrocardiology* 37.3 (2004): 219-225.

22. Jenkins D., *et al*. "State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management". *European Respiratory Review* 21.123 (2012): 32-39.

23. Jaff MR., *et al*. "Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension". *Circulation* 123.16 (2011): 1788-1830.

24. Irene Marthe Lang and Michael Madani. "Update on Chronic Thromboembolic Pulmonary Hypertension". *Circulation* 130.6 (2014): 508-518.

25. "Guidelines for the diagnosis and treatment of pulmonary hypertension The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)". *European Heart Journal* 30.20 (2009): 2493-2537.

26. Fedullo P., *et al*. "Chronic thromboembolic pulmonary hypertension". *American Journal of Respiratory and Critical Care Medicine* 183.12 (2011): 1605.

27. Andreassen AK., *et al*. "Balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension". *Heart* 99.19 (2013): 1415-1420.

28. McNeil K and Dunning J. "Chronic thromboembolic pulmonary hypertension (CTEPH)". *Heart* 93.9 (2007): 1152-1158.

29. Piazza G and Goldhaber SZ. "Chronic thromboembolic pulmonary hypertension". *New England Journal of Medicine* 364.4 (2011): 351-360.

30. Coghlan G., *et al*. "Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland". *Thorax* 63.2 (2008): ii1.

31. Makowski CT., *et al*. "Riociguat: a novel new drug for treatment of pulmonary hypertension". *Pharmacotherapy* 35.5 (2015): 502-519.

32. Ghofrani HA., *et al*. "Riociguat for the treatment of chronic thromboembolic pulmonary hypertension". *New England Journal of Medicine* 369.4 (2013): 319-329.

33. Rich S. "Primary pulmonary hypertension: executive summary". Evian, France. World Health Organization (1998).

34. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th edition, Little, Brown & Co, Boston (1994): 253.

35. Hughes RJ., *et al*. "The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study". *European Respiratory Journal* 28.1 (2006): 138-143.

36. Ghofrani HA., *et al*. "Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study". *European Respiratory Journal* 36.4 (2010): 792-799.

37. Suntharalingam J, *et al*. "Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension". *Chest* 134.2 (2008): 229.

38. Ghofrani HA., *et al*. "Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension". *Annals of Internal Medicine* 136.7 (2002): 515.

39. Nagaya N., *et al*. "Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension". *Chest* 123.2 (2003): 338-343.

40. Jensen KW., *et al*. "Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy". *Circulation* 120.13 (2009): 1248-1254.

41. Kim NH., *et al*. "Chronic thromboembolic pulmonary hypertension". *Journal of the American College of Cardiology* 62.25 (2013): D92-D99.

42. Corsico AG., *et al*. "Long-term outcome after pulmonary endarterectomy". *American Journal of Respiratory and Critical Care Medicine* 178.4 (2008): 419-424.

43. Mo M., *et al*. "Reoperative pulmonary thromboendarterectomy". *Annals of Thoracic Surgery* 68.5 (1999): 1770-1777.

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