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Chronic Thromboembolic Pulmonary Hypertension (CTEPH): A Review

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease classified by the World Health Organization (WHO) as Group IV Pulmonary Hypertension (PH) and is thought to result from persistent or recurrent pulmonary emboli.[1] CTEPH is defined from the most recent 6th World Symposium on Pulmonary Hypertension (WSPH) as mean pulmonary artery pressure (mPAP) > 20 mmHg (updated from 25 mm Hg from the 5th WSPH), and mean pulmonary arterial wedge pressure (mPAWP) </= 15mmHg as measured by right heart catherization (RHC)* in the presence of chronic/organized flow-limiting thrombi/emboli in the pulmonary arteries (PAs) after at least 3 months of effective anticoagulation therapy.1 CTEPH is thought to be underdiagnosed because most patients are diagnosed in WHO Functional Class (FC) III and IV. Because CTEPH is one of the 5 main diagnostic categories of PH, it's imperative to distinguish it from the other groups of PH, based on cause, pathophysiology, clinical presentation, and treatment options, to diagnose and treat it appropriately.[1] Currently, CTEPH is the only PH subgroup with a potential cure without lung transplantation. This article addresses what is known about CTEPH, its treatment, and related nursing implications.

Incidence and Prevalence

Determining the true incidence of CTEPH is difficult because most patients with an acute pulmonary embolus (PE) do not undergo routine follow-up assessment of pulmonary pressures or repeat imaging. As well, a surprisingly large proportion (25%–67%) of patients with CTEPH cannot remember a history of venous thromboembolism (VTE) or PE.[2,3] In addition, reported rates vary widely, possibly related to differences in the patient populations studied and the methods of calculating rates. Available data indicate that CTEPH is rare, occurring in only a small proportion (0.5%–3%) of those who survive a PE.[5] In an analysis of 25 publications and 14 databases conducted in the United States and Europe, the crude annual full incidence of CTEPH (diagnosed and undiagnosed) was 3 to 5 cases per 100,000 population.[6] 75% of patients with CTEPH had a documented history of acute PE.[7] Incidence of CTEPH after asymptomatic acute PE is reported to range from 0.1% to 11.8%.[4] Other estimates suggest that for patients surviving a PE, approximately 4% will go on to develop CTEPH.[8] Overall the prevalence of CTEPH has been reported to be up to 38.4 per million individuals.[2,9]

Unlike other PH subgroups, in CTEPH men and women are equally affected with most registries reporting approximately equal numbers of both sexes. Most cases occur in the 6th decade of life and according to the 2007 to 2009 International CTEPH Registry (679 newly diagnosed patients < 6 months) about 75% had previous PE.[1,3,10]

Risk Factors

As noted, CTEPH may develop after an acute thromboembolic event. It can remain asymptomatic for months. At diagnosis all patients are symptomatic, and most will be

* Pulmonary vascular resistance (PVR) >/= 3 Woods unit, a calculated value from the RHC is also included in definition.

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diagnosed within 2 years.[11,12] CTEPH has been correlated with coagulation abnormalities and chronic inflammatory disorders. Previous splenectomy, ventriculoatrial shunt, and infected pacemaker are other independent predictors of CTEPH.[3] Recently, thyroid replacement therapy and malignancy have been reported as risk factors as well. In a prospective long-term follow-up study, Pengo identified several factors that were associated with increased risk of CTEPH, including recurrent PE, younger age, larger perfusion defects, idiopathic presentation, elevated factor VIII, dysfibrinogenemia, antiphospholipid antibodies, and lupus anticoagulant.[13]

However, many patients with CTEPH will have no clear history of an acute deep vein thrombosis (DVT) or PE, and may present these patients may present with worsening shortness of breath on exertion. Only after a workup for PAH are they diagnosed with CTEPH.[14]

CTEPH Pathogenesis

The pathogenesis of CTEPH has not been fully elucidated.[6] However, it is believed that CTEPH results from chronic thromboembolic occlusion of the proximal or distal pulmonary vasculature.[15] Over time, resistance to blood flow through the pulmonary arteries increases, resulting initially from obstruction of pulmonary arterial vessels by organized thromboembolic material and subsequently from vascular remodeling in small unobstructed vessels.[15] Small vessel disease in CTEPH may result from overperfusion of nonoccluded lung areas; this disease presents histological similarities with the pulmonary arteriopathy of idiopathic pulmonary artery hypertension (IPAH).[3] Acute pulmonary embolism may also initiate CTEPH.[7] Histological examination of resected vascular sections during pulmonary endarterectomy showed organized thrombi of uniform age in most cases, suggesting that a single incompletely resolved thromboembolic event was responsible for the initiation of the disease. In all specimens, intimal thickening with collagen deposition, inflammation, atherosclerosis, and calcification was seen.[14]

Diagnosis

CTEPH is underdiagnosed, perhaps because patients are not referred to an expert center or are misdiagnosed. The diagnosis of CTEPH is complex. Patient history is important but may not be conclusive some patients do not report a PE history. Patients will present early with exertional dyspnea and later, will have evidence of exertional dyspnea. Late in the disease, evidence of right heart dysfunction, such as chest discomfort and syncope, may manifest.[12]

On physical exam, patients may display typical findings of PAH and right heart dysfunction, such as jugular venous pressure, tricuspid regurgitation murmur, loud pulmonic component of the second heart sound, and peripheral edema. Pulmonary bruits may predict proximal disease with turbulent flow.[12] The ECG may be normal or may show right-sided abnormalities. Chest x-ray and echocardiogram may also reveal abnormalities.

Hemodynamic parameters must indicate PH; then mismatched perfusion defects must be verified through additional testing. All CTEPH patients should be assessed with a right heart catheterization, the gold standard for hemodynamic assessment, to provide accurate prognostic information. A ventilation/perfusion (V/Q) lung scan is performed early in the diagnostic workup. While a low probability scan rules out the diagnosis, a high probability scan demonstrates multiple mismatched segmental perfusion defects. Once the disease is diagnosed, surgical accessibility must be determined. Additional tests including pulmonary angiography, MRI pulmonary angiography, and computed tomographic pulmonary angiography (CTPA) will determine if the patient is a surgical candidate.

Treatment

Untreated CTEPH patients have a poor prognosis, with the 5-year survival rate reported at 30% if mPAP > 40 mm Hg, and only 10% if the mPAP is > 50 mm Hg.[16] Management of the disease has progressed in recent years, and there are several options for cure or treatment. For patients with operable disease, the treatment of choice is pulmonary endartertectomy (PEA).

Pulmonary Endartertectomy

PEA is the only curative treatment option to date.[7,17] It is a complex surgery involving the surgical removal of chronic thromboembolic obstructions, which requires cardiopulmonary bypass, induced hypothermia, and circulatory arrest. Therefore, only experienced CTEPH teams can perform this surgery. When PEA is performed by experienced CTEPH teams, the procedure has an operative mortality of approximately 5% with estimated 1-year and 10-year survival of 90% and 70%, respectively.[18]

Operability

Operability assessment is critical. An expert center is highly recommended to evaluate the patient and to perform surgery, if indicated. Operability of patients with CTEPH is determined by multiple, complex factors that cannot easily

be standardized.[17] General criteria for operability include severity as determined by WHO FC II-IV and surgical accessibility of the occluded pulmonary arteries—proximal arteries are accessible, while distal arteries are not. Advanced age alone is not a contraindication for surgery.[18] PEA is the gold standard and may be curative for those patients with operable CTEPH, improves survival and quality of life, but not all patients are surgical candidates. Inaccessible clots and patient comorbidities preclude PEA.[11] About 62% of patients are considered eligible for PEA.[17] But some patients who may be surgical candidates refuse surgery because of or inability to travel to a CTEPH. Of eligible patients, approximately 17% refuse surgery because of its associated risks. This represents 9% of all CTEPH patients.[9] For those patients who are deemed nonoperable, have significant comorbidities that preclude PEA surgery, or simply refuse PEA surgery, a procedure known as balloon pulmonary angioplasty (BPA) and targeted medical therapy may be considered.

Balloon Pulmonary Angiography

BPA is an emerging and increasingly performed therapeutic option for inoperable CTEPH patients.[17] BPA is a surgical technique in which serial and progressive dilation of stenotic pulmonary arteries during angiography reduces obstructions and improves blood flow in the pulmonary vasculature.[1] Unlike cardiac revascularizations in which clinical improvement can be seen after the revascularization of a single vessel, clinical improvement following BPA is typically observed after several revascularization procedures of multiple diseased segments.

Overall, BPA is associated with improvements in cardiopulmonary hemodynamics, pulmonary perfusion, exercise tolerance, functional class, and 6-minute walk distance test. However, improvement in pulmonary hypertension may take a few weeks or more. Although data on long-term outcomes of BPA in CTEPH are limited, persistence of hemodynamic benefit (reduction in PVR and PAP) 2 years after procedure completion has been observed.[11]

Pharmacologic Therapy

Pharmacologic intervention using PAH-specific therapies is an important aspect of treatment for inoperable CTEPH patients.[11,17] Lifelong anticoagulation is recommended in all patients with CTEPH.[17] The aim of anticoagulation is to prevent pulmonary artery thrombosis and recurrent VTE. In clinical practice, patients not suitable for surgery are considered for management with PAH-targeted therapies. Both clinical and pathologic similarities exist between PAH and CTEPH suggest that PAH-targeted therapies may be helpful.

Riociguat is a soluble guanylate cyclase (sGC) stimulator indicated for use in PAH and for patients with inoperable and persistent or recurrent CTEPH after PEA. In the Phase 3, 16-week, double-blind, randomized placebo-controlled CHEST-1 (CHronic ThromboEmbolic Pulmonary Hypertension sGC-Stimulator Trial) with 216 patients, riociguat was associated with significant improvements in exercise capacity, PVR, N-terminal prohormone brain natriuretic peptide (NT-pro BNP), WHO FC, Borg dyspnea index, and quality of life (QoL). Riociguat is orally administered 3 times daily and requires an 8-week titration period with multiple dose adjustments before reaching the maintenance dosage.[19] Although no other PAH-targeted therapy is currently approved for treatment of CTEPH, several clinical trials have been conducted in patients with CTEPH using PAH-specific medications. Macitentan, an endothelin receptor antagonist (ERA), was studied in a placebo-controlled trial in patients with inoperable CTEPH. MERIT-1 (Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension)[20] was a phase 2 trial that enrolled 80 inoperable patients. The concurrent use of phosphodiesterase type–5 inhibitors and oral or inhaled prostanoids were allowed. The primary endpoint was PVR at 16 weeks of treatment. Those in the macitentan group demonstrated a reduction in pulmonary vascular resistance (PVR) of 73% of baseline compared with 87.2% for those receiving placebo. Six-minute walk distance (6MWD) at 24 weeks increased by a mean of 35 meters in the macitentan group compared with 1 meter in the placebo patients.

Bosentan was studied in the BENEFiT (Bosentan Effects in iNopErable Forms previously of chronic Thromboembolic pulmonary hypertension).[21] Although there was a significant 24% reduction in PVR after 16 weeks of treatment (-146 dyn·s·cm–5; $P < 0.0001$) in one of the co-primary endpoints, there was no change in the 6MWD (+2.2 m; $P = 0.5449$).

Lastly, a study with ambrisentan, the AMBER (A Randomised, Multicentre, Double-Blind, Placebo-Controlled Study of Ambrisentan in Subjects With Inoperable Chronic Thromboembolic Pulmonary Hypertension) trial was started but was stopped before completion because of low patient enrollment.[22]

Nursing Implications

The nurse has a significant role working with patients with CTEPH in monitoring, support, and education.

Monitoring

Patients with an acute PE or VTE should be monitored for the subsequent development of CTEPH. High-risk factors in these patients have been identified. The group of patients at highest risk includes patients with major central thromboembolic events, those presenting with significant hemodynamic disturbance or evidence of right ventricular dysfunction, patients with documented thrombophilia, and patients with persistent abnormalities of lung perfusion on follow-up testing.[14] These patients should probably be followed regularly for up to 2 years.

Support

Nurses must provide supportive care for those patients who are compromised because of sickness and fear who must now undergo a series of tests they do not understand. Moreover, they certainly may fear the results. If a diagnosis of CTEPH is proven, the nurse can provide support during decision making about appropriate treatment. Additionally, the nurse is in an ideal position to assist the patients through referrals to other providers (eg, social workers) or programs (eg, financial) that may be able to assist with the patient's needs. The nurse also can support the patient through the cumbersome titration process if medical therapy is required.

Education

A primary role of the nurse is as an educator. The nurse is an interpreter—translating medical terminology into language that a patient can understand, keeping in mind that adult learners learn best in the context of problem solving. Put differently, the nurse can help the patient relate what is being taught to how it may help them to breathe and function better now and in the future. Once the diagnosis has been provided the nurse can become a valued partner throughout the process of making treatment decisions and manging their disease. ■

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Chronic Thromboembolic Pulmonary Hypertension (CTEPH): A Review

Questions

1. Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to result from persistent or recurrent pulmonary emboli.

a. True b. False

2. Currently CTEPH is the only pulmonary hypertension subgroup with a potential cure without lung transplantation.

a. True b. False

3. The crude annual full incidence of CTEPH is the US is how many cases per 100,000 population?

a. 1–2 cases
b. 2–4 cases
c. 3–5 cases
d. 4–6 cases

4. Men and women are equally affected with CTEPH.

a. True b. False

5. Risk factors for CTEPH include:

a. Coagulation abnormalities
b. Chronic inflammatory disorders
c. Previous splenectomy
d. All of the above

6. Although the diagnosis of CTEPH is complex, the physical exam may show:

a. Jugular venous pressure
b. Tricuspid regurgitation murmur
c. Peripheral edema
d. All of the above

7. For those patients with operable disease, the treatment of choice is:

a. Pharmacologic therapy
b. Pulmonary endarterectomy
c. Balloon pulmonary angiography
d. None of the above

8. Lifelong anticoagulation is recommended in all patients with CTEPH.

a. True b. False

9. Patients with an acute PE or VTE should be monitored for subsequent development of CTEPH.

a. True b. False

10. Education plays an important role for the patient with CTEPH.

a. True b. False

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Chronic Thromboembolic Pulmonary Hypertension (CTEPH): A Review

Answers

April 2019

1. Define chronic thromboembolic pulmonary hypertension (CTEPH). _____

2. State three risk factors for CTEPH. _____

3. State three forms of treatment for CTEPH. _____

Please indicate your answer by filling in the letter:

1. _____ **2.** _____ **3.** _____ **4.** _____ **5.** _____ **6.** _____ **7.** _____ **8.** _____ **9.** _____ **10.** _____

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