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SPECIAL ARTICLE

Brazilian Thoracic Society recommendations for the diagnosis and treatment of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious and debilitating disease caused by occlusion of the pulmonary arterial bed by hematic emboli and by the resulting fibrous material. Such occlusion increases vascular resistance and, consequently, the pressure in the region of the pulmonary artery, which is the definition of pulmonary hypertension. The increased load imposed on the right ventricle leads to its progressive dysfunction and, finally, to death. However, CTEPH has a highly significant feature that distinguishes it from other forms of pulmonary hypertension: the fact that it can be cured through treatment with pulmonary thromboendarterectomy. Therefore, the primary objective of the management of CTEPH should be the assessment of patient fitness for surgery at a referral center, given that not all patients are good candidates. For the patients who are not good candidates for pulmonary thromboendarterectomy, the viable therapeutic alternatives include pulmonary artery angioplasty and pharmacological treatment. In these recommendations, the pathophysiological bases for the onset of CTEPH, such as acute pulmonary embolism and the clinical condition of the patient, will be discussed, as will the diagnostic algorithm to be followed and the therapeutic alternatives currently available.

Keywords: Hypertension, pulmonary/diagnosis; Hypertension, pulmonary/surgery; Hypertension, pulmonary/therapy; Hypertension, pulmonary/drug therapy; Pulmonary artery/pathology; Pulmonary embolism/complications.

DEFINITION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) that results from occlusion of the pulmonary circulation by residual organized thromboembolic material, with consequent pulmonary microvasculature remodeling, which is induced or enhanced by a combination of imperfect angiogenesis, reduced endogenous fibrinolysis, and endothelial dysfunction. In this process, there is a gradual replacement of the normal intimal endothelial layer, causing a reduction in the pulmonary vascular bed and a consequent increase in its resistance and, therefore, in the afterload of the right ventricle. The increased load imposed on the right ventricle leads to progressive right ventricular failure, which is the major factor responsible for the mortality associated with CTEPH.[1]

The definition of CTEPH is based on objective criteria (Chart 1).[2] Conceptually, the diagnostic criteria aim to exclude a potential component related to acute embolic material (hence the requirement of at least three months of full anticoagulation), to confirm occlusion with imaging methods (rather than only on the basis of clinical suspicion), and, finally, to confirm the presence of PH. It is important to understand this concept in the broader context of other causes of PH.

Multiple etiological processes may be responsible for the elevation of pressure in the pulmonary vascular system as opposed to the normal condition of low pressure and low vascular resistance. By definition, PH occurs when mean pulmonary artery

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Chart 1. Diagnostic criteria for chronic thromboembolic pulmonary hypertension (all are required).

Diagnostic criterion
Invasive confirmation of pulmonary hypertension: mean pulmonary artery pressure > 20 mmHg[a]
Confirmation of pulmonary thromboembolism by pulmonary artery CT angiography, ventilation/perfusion lung scintigraphy, or pulmonary arteriography
At least three months of effective anticoagulation

Adapted from Galiè et al.[2] [a]Simonneau et al.[3]

pressure (mPAP) exceeds 20 mmHg.[3] This pressure threshold for defining PH has recently been set; most evidence regarding all forms of PH considers an mPAP ≥ 25 mmHg as a diagnostic criterion. Therefore, although the present recommendations adopt the current criterion for defining PH, it should be understood that the scientific evidence is quite limited in patients with an mPAP between 21 and 24 mmHg.

There are various pathophysiological mechanisms that might cause PH: increased pulmonary vascular hydrostatic pressure, as in mitral stenosis; vascular bed loss associated with hypoxic vasoconstriction, as in lung parenchymal diseases; pulmonary vascular remodeling with endothelial and middle layer proliferation, as in idiopathic pulmonary arterial hypertension (PAH); or even mechanical obstruction of the vascular bed, as previously mentioned in CTEPH.[4] Therefore, the first step in dealing with a patient with PH is to determine the predominant pathophysiological mechanism. This will allow adequate classification of the patient according to the current system (Chart 2), which is based on grouping patients by the major pathophysiological mechanism, clinical presentation, and response to treatment; that is, when a patient with PH is adequately classified, there is an associated treatment plan available.[3]

In accordance with the current classification of PH, CTEPH is in group 4.[3] As previously mentioned, adequate classification of CTEPH is particularly significant, because the therapeutic approach to CTEPH is completely different from that to other forms of PH, given that surgical treatment might be curative.[5]

PATHOPHYSIOLOGY: FROM ACUTE PULMONARY THROMBOEMBOLISM TO CTEPH

In up to approximately 80% of the cases of CTEPH, the disease is preceded by an identified episode of acute pulmonary thromboembolism (PTE).[6] During the acute event, there are several changes resulting from the presence of emboli, changes that are outside the scope of these recommendations.[7] However, it is worth noting that an acute PTE episode can have three possible clinical outcomes[8]: 1) right ventricular failure due to an acute increase in the afterload of the right ventricle, which can lead to death; 2) complete reperfusion of the pulmonary circulation in the medium term, which can be spontaneous (resulting from the action of endogenous thrombolytics) or secondary to treatment; or 3) partial reperfusion of the pulmonary circulation, with residual occlusion of part of the pulmonary circulation. It is believed that one year after an acute PTE episode adequately treated with anticoagulants, approximately 30% of patients will continue to have filling defects in the pulmonary circulation when reevaluated with ventilation/perfusion lung scintigraphy,[9] although not all of those will be symptomatic. Patients with perfusion defects after an episode of acute pulmonary embolism who continue to have dyspnea but do not have PH at rest are classified as having chronic pulmonary thromboembolic disease (CPTED).[1] In this group, symptoms are due to PH on exertion or to changes in ventilation and gas exchange. In contrast, patients with residual perfusion defects, symptoms of even greater relevance, and PH are characterized as having CTEPH.

Unlike patients with CPTED, patients with CTEPH have marked hemodynamic dysfunction not only because of the hypoperfused vascular region (due to chronic pulmonary artery occlusion), but also because of clot-free lung regions, which are subjected to relatively increased flow, given that the blood flow diverted from the obstructed regions.[10] In addition, it is speculated that bronchial circulation, whose flow is increased in such cases, may also lead to further increased flow in the vascular bed distal to the obstruction because of the presence of collateral circulation. This increased flow leads to endothelial dysfunction, with consequent vascular remodeling.

As a result of this condition of regional hypoperfusion/increased flow, susceptible patients develop PH and subsequent right ventricular failure. Therefore, endothelial dysfunction in CTEPH is found not only in the pulmonary artery region but also in the capillary and venous regions.[11] This could explain why a considerable number of patients continue to have residual PH after pulmonary thromboendarterectomy (PTEA),[12] a surgical procedure that is intended to cure CTEPH but that would not interfere with the disease affecting the pulmonary capillary and venous systems because it addresses only the fibrous material that is obstructing the pulmonary arteries.

EPIDEMIOLOGY

The prevalence of CTEPH after acute PTE is highly debatable, with rates ranging from 0.7% to 10% in the literature.[13-15] A meta-analysis of 16 studies, involving 4,407 patients followed for more than two years, reported an overall incidence of 0.56% (95% CI: 0.1-1.0%). When only the patients who survived for at least six months after the embolic event were considered, the incidence was 3.2% (95% CI:

Chart 2. Current classification of pulmonary hypertension.

Classification of pulmonary hypertension
1. Pulmonary arterial hypertension
1.1 Idiopathic pulmonary arterial hypertension
1.2 Heritable pulmonary arterial hypertension
1.3 Drug- or toxin-induced pulmonary arterial hypertension
1.4 Pulmonary arterial hypertension associated with:
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.5 Responders to calcium channel blockers
1.6 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1.7 Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Heart failure with preserved EF
2.2 Heart failure with reduced EF
2.3 Valvular disease
2.4 Congenital or acquired heart diseases leading to post-capillary pulmonary hypertension
3. Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung diseases with mixed restrictive and obstructive patterns
3.4 Hypoxia without structural lung disease
3.5 Lung developmental disorders
4. Pulmonary hypertension due to pulmonary artery obstructions
4.1 Pulmonary hypertension due to chronic pulmonary thromboembolism
4.2 Other pulmonary artery obstructions: sarcoma or angiosarcoma; other malignant tumors (renal carcinoma, uterine carcinoma, gem cell tumors of the testis); non-malignant tumors (leiomyoma); arteritis without connective tissue disease; congenital pulmonary artery stenoses; parasitosis (hydatidosis)
5. Pulmonary hypertension due to unclear and/or multifactorial mechanisms
5.1 Hematological disorders: chronic hemolytic anemia; myeloproliferative disorders
5.2 Systemic and metabolic disorders: pulmonary Langerhans cell histiocytosis; Gaucher disease; glycogen storage disease; neurofibromatosis; and sarcoidosis
5.3 Others: fibrosing mediastinitis; chronic renal failure with or without hemodialysis
5.4 Complex congenital heart disease

Adapted from Simonneau et al.[3] EF: ejection fraction.

2.0-4.4%), and, among these patients, when only those without major comorbidities were considered, the incidence was 2.8% (95% CI: 1.5-4.1%).[16] The incidence of CTEPH in the global population is reported to be 5 new cases/million population per year,[17] the mean age at diagnosis being 63 years and men and women being equally affected.[18] Time to diagnosis is long, having been reported to be, on average, 14 months in a European cohort.[19]

Contrary to what might be supposed, the risk factors for CTEPH are different from the classic predisposing factors for acute PTE, which have been associated with the classic triad described by Virchow: hypercoagulability; endothelial lesion; and venous stasis.[20] Deficiencies of antithrombin, protein C, and protein S, as well as factor V Leiden mutation, have not been associated with the presence of CTEPH.[21] However, high serum concentrations of factor VIII and the presence of lupus anticoagulant and antiphospholipid antibodies have been associated with the development of CTEPH, as has the presence of genetic variants that lead to fewer sites of binding of clots to plasmin, making the thrombi more resistant to lysis by endogenous thrombolytics.[22] The identification of familial clusters of CTEPH cases has also corroborated the role of genetic changes in the genesis of this disease.[23]

Various clinical comorbidities have also been associated with CTEPH: neoplasms; arteriovenous shunts; splenectomy; and chronic inflammatory diseases (such as inflammatory bowel disease, osteomyelitis, and rheumatoid arthritis).[24-26] Very curiously, chronic infectious diseases, particularly bacterial ones, associated with infection with *Staphylococcus aureus*, appear to be related to the development of CTEPH. Fragments of *S. aureus* DNA have been isolated in the peripheral blood of patients with CTEPH, but not in patients with acute PTE.[27] The greatest risk factor for the development of CTEPH in a European cohort was infection of cardiac pacemakers.[24] In addition, in experimental models, the presence of *S. aureus* resulted in delayed recanalization of induced thrombi.[27] Thyroid dysfunction, particularly that caused by thyroid hormone replacement therapy, has been identified as an independent risk factor for CTEPH. A recent study identified thyroid dysfunction in 10.5% of the patients with scheduled surgery, and, in 54.8% of those patients, there was no history of

thyroid disease.[28] Elevated levels of (endogenous or exogenous) thyroid hormones are associated with a higher risk of thrombosis secondary to an increase in factor VIII and von Willebrand factor, as well as with deficient fibrinolysis. The major risk factors for the development of CTEPH are described in Table 1.

DIAGNOSIS

The diagnosis of CTEPH is based on clinical status, imaging studies, and hemodynamic data. The main complaint is progressive dyspnea, most often preceded by an episode of acute PTE or deep vein thrombosis in the lower limbs. Physical examination can reveal a loud pulmonary component of the second heart sound and signs of right heart failure, with leg edema, ascites, and jugular stasis. Episodes of syncope may also be present. Hemoptysis is a more common symptom than in other forms of PH, being secondary to rupture of hypertrophied bronchial arteries.[29]

Chest X-ray is of very limited importance in assessing CTEPH because it yields nonspecific findings, and echocardiography is commonly used as a screening test to investigate the presence of PH. One of the tests that can add sensitivity to the diagnosis of PH is cardiopulmonary exercise testing (CPET). CPET seeks to identify changes in oxygen consumption and carbon dioxide output during exercise, identifying the mechanism causing dyspnea; in early cases of PH, CPET can identify exertional limitation and increased physiological dead space.[30]

Ventilation/perfusion lung scintigraphy (Figure 1) remains to be the test of choice for the investigation of cases of suspected CTEPH because of its high sensitivity (96-97%) and high specificity (90-95%),[31] both of which are higher than those of conventional CT angiography (Figure 2). A meta-analysis evaluating CT angiography for the diagnosis of CTEPH reported an aggregate sensitivity of 76% (95% CI: 69-82%), despite a high specificity of 96% (95% CI: 93-98%).[32] Low probability scintigraphic findings exclude the diagnosis of CTEPH, which is not true for conventional CT angiography. More recent techniques, such as dual-energy CT angiography with iodine maps, have shown sensitivity and specificity similar to those of lung scintigraphy.[33]

The most significant role of chest CT angiography is the diagnosis of acute PTE. In CTEPH, the greatest importance of chest CT angiography does not lie in excluding the diagnosis, but rather in making the differential diagnosis of CTEPH from other causes of vascular obstruction,[34] as well as from lung parenchymal changes that might suggest the presence of heterogeneous perfusion (Figure 3). In addition, chest CT angiography has been a strategic tool for evaluating treatment options for CTEPH, together with lung scintigraphy and digital pulmonary angiography. In conjunction with hemodynamic data, these tests can define the best therapeutic strategy: PTEA, considered the treatment of choice; balloon pulmonary angioplasty (BPA); or pharmacological treatment.

Chest CT angiography can also be useful in differentiating between acute PTE and CTEPH. There are radiological signs of chronicity of pulmonary vascular impairment that are identifiable on CT angiography and that make it possible to prevent inappropriate use of treatments for primary pulmonary reperfusion injury (thrombolytics or embolectomy)[35,36] in cases initially diagnosed as acute events (Chart 3). Only patients with acute PTE and signs of hemodynamic instability should receive these treatments,[8,37] not those with newly diagnosed CTEPH.

Magnetic resonance imaging (MRI) can be used for the differential diagnosis of CTEPH (from pulmonary artery sarcoma, for instance).[38] In addition, cardiac MRI provides reliable information on cardiac chambers, allowing prognostic evaluation and the follow-up of interventions such as PTEA.[39] Pulmonary artery magnetic resonance angiography is not usually used for the diagnosis of CTEPH for reasons of spatial resolution and logistics, although new techniques and equipment have improved its accuracy.[40]

Similarly to MRI, positron-emission tomography-CT (PET-CT) can contribute to the differential diagnosis of CTEPH from diseases mimicking CTEPH. The role of PET-CT has been described in the identification of pulmonary artery sarcomas[41] and Takayasu's arteritis involving the pulmonary arteries.[42] In both conditions, the uptake of glucose labeled with ^{18}F-fluorodeoxyglucose measured with PET-CT is substantially increased in the vascular obstruction

Table 1. Major risk factors for the development of chronic thromboembolic pulmonary hypertension.

Risk factor	OR (95% CI)
Infected pacemaker/arteriovenous shunts	76.40 (7.67-10.351)
Splenectomy	17.87 (1.56-2.438)
Recurrent venous thromboembolism events	14.49 (5.4-43.08)
Thyroid hormone replacement therapy	6.10 (2.73-15.05)
Previous venous thromboembolism event	4.52 (2.35-9.12)
Antiphospholipid antibodies and lupus anticoagulant antibodies	4.20 (1.56-12.21)
History of malignancy	3.76 (1.47-10.43)
Blood type other than O	2.09 (1.12-3.94)

Based on data from Bonderman et al.[24],[a] [a]Independent risk factors when compared with those of patients with nonthromboembolic pulmonary hypertension; in that study,[24] most patients had pulmonary arterial hypertension (group 1).

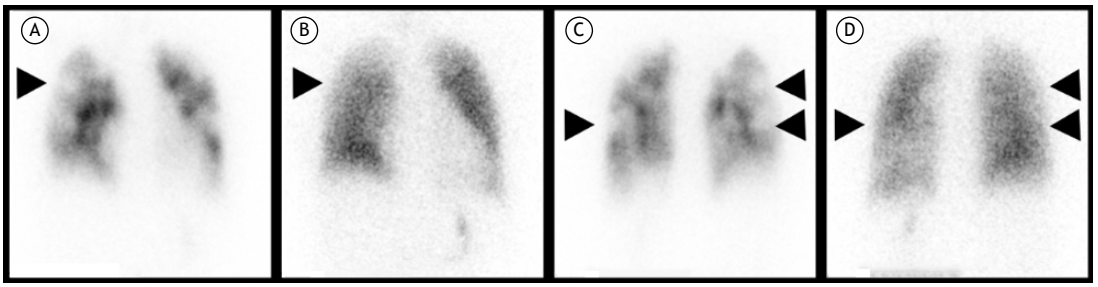

Figure 1. Ventilation/perfusion scintigraphy of a patient with chronic thromboembolic pulmonary hypertension. Note that ventilation is homogeneous (B and D), but perfusion is heterogeneous, with several segmental defects (A and C). There are regions that receive ventilation but not perfusion (arrowhead), suggesting vascular occlusion.

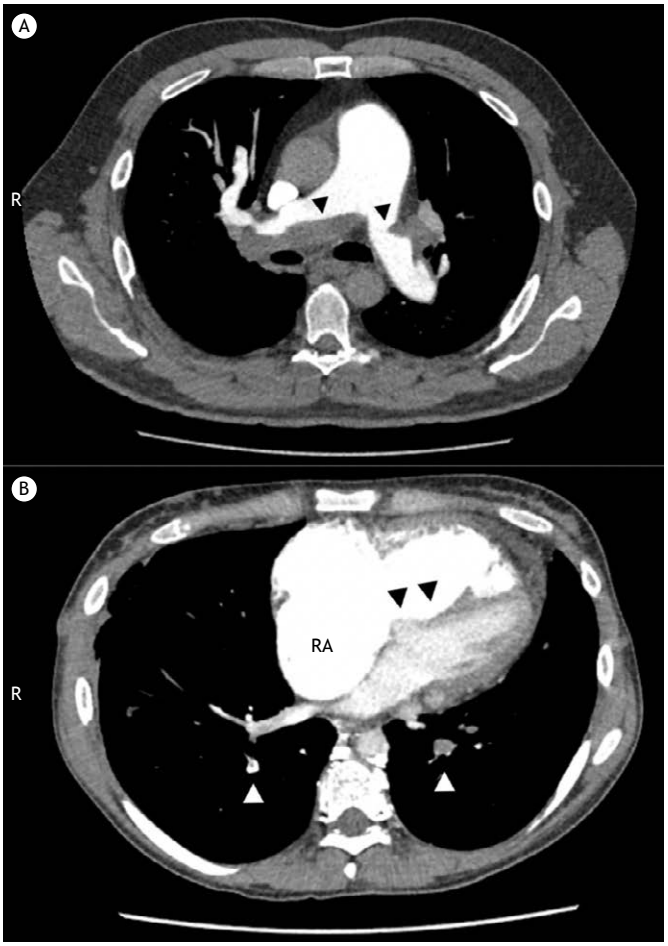

Figure 2. Chest CT angiography of a patient with chronic thromboembolic pulmonary hypertension. Note in A the eccentric clots that adhere to the pulmonary artery walls; in B, in addition to the clots, the dilated right atrium (RA) and the flattening of the interventricular septum (black arrowheads), suggesting pulmonary hypertension and right ventricular dysfunction.

and distinguishes these conditions from CTEPH, given that the vascular occlusions in CTEPH generally do not show uptake of labeled glucose on PET-CT.

Invasive tests, such as right heart catheterization (RHC) and digital subtraction pulmonary arteriography (Figure 4), are key to preoperative assessment and to stratification of clinical and surgical risk in patients with CTEPH. RHC is mandatory to confirm the presence of PH, typically precapillary PH.[1] Although some patients with CTEPH may show vasoreactivity, which may indicate a better prognosis, RHC is not performed at the treatment level, because it does not alter therapy.[2,43] Given the complexity of these tests and their importance in defining the therapeutic approach, they should be performed at referral centers for CTEPH. The sequence of tests recommended for the investigation of CTEPH can be seen in Figure 5.

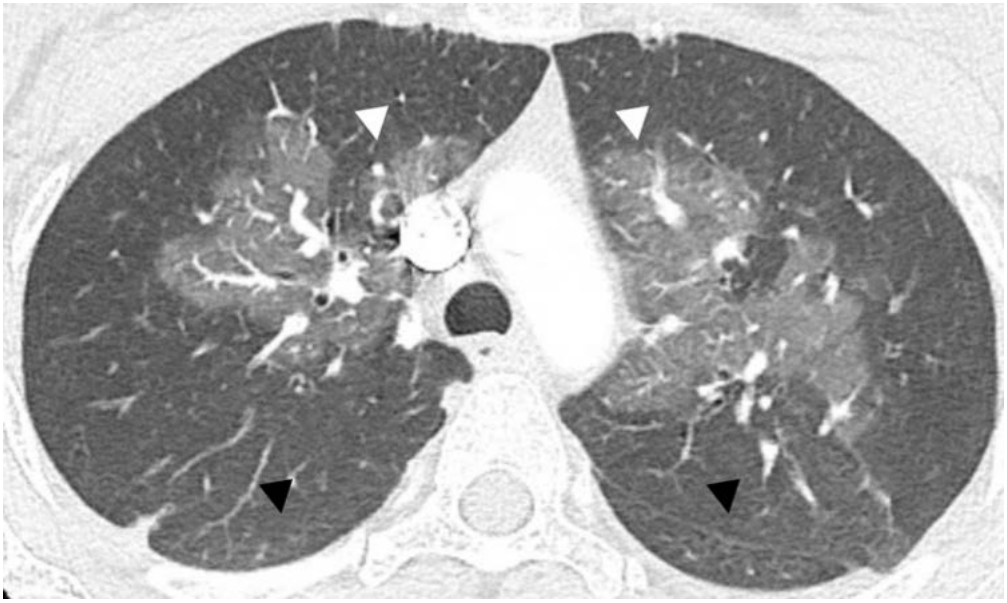

Figure 3. CT image on lung parenchymal window setting in a patient with chronic thromboembolic pulmonary hypertension. Note the mosaic perfusion pattern, with hypoperfused areas (black arrowheads) and hyperperfused areas (white arrowheads).

Chart 3. Pulmonary artery CT angiography findings suggestive of pre-existing chronic vascular disease.

Direct vascular signs
Eccentric filling defects that adhere to the vascular wall and may show calcification, being different from filling defects in the center of blood vessels, within the dilated lumen, which are suggestive of acute pulmonary thromboembolism Abrupt termination of a vessel Complete vascular occlusion or concave or pouch-like filling defects Intimal irregularity Linear intraluminal filling defects (such as bands or webs) Stenosis or poststenotic dilatation Vascular tortuosity
Indirect vascular signs
Significant right ventricular hypertrophy, right atrial dilatation Pericardial effusion Pulmonary arterial dilatation (> 29 mm in men and > 27 mm in women) or pulmonary arterial wall calcification Poststenotic dilation of bronchial arteries resulting from obstructed vessels
Parenchymal changes
Mosaic attenuation of the parenchyma as a consequence of geographic variation in perfusion

Modified from Dias et al.[34]

Regardless of the imaging method used, it is important to consider other diagnoses that can mimic CTEPH. As highlighted above, differentiation from acute PTE should always be sought. Large unilateral filling defects and/or intravascular lobulation suggest pulmonary artery sarcomas. The presence of multiple aneurysms and/or arterial wall thickening should raise the suspicion of pulmonary arterial vasculitis. Sometimes, abrupt termination of a major branch of the pulmonary artery, the causes of which can be a central thrombus, hypoplasia, or agenesis of the pulmonary artery, can be a diagnostic challenge. Large thrombi in situ, especially at bifurcation of pulmonary arteries and their branches, occurring more frequently in conditions of increased flow, such as in congenital heart disease with shunt, can also cause diagnostic difficulties in CTEPH.[38]

TREATMENT OF CTEPH

General approach

Some approaches suggested for other forms of PH are also recommended for patients with CTEPH, although most of them have a low level of evidence. Chief among them are[2]: 1) female patients should avoid pregnancy and should be enrolled in specific education and follow-up programs, given the increased complexity associated with the use of hormonal contraceptive methods in this population; 2) physical

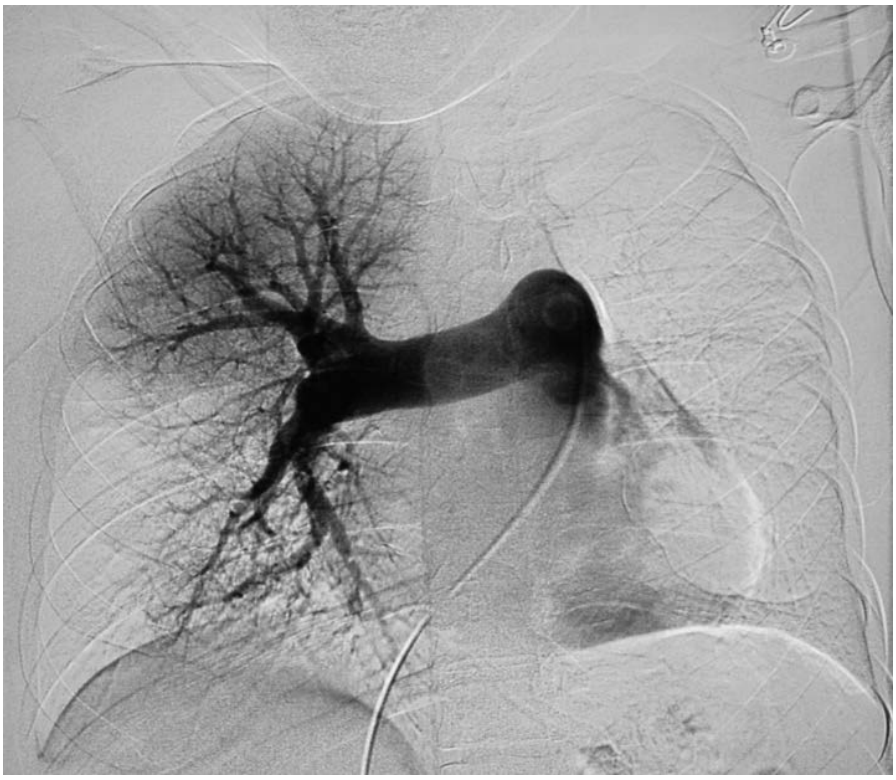

Figure 4. Pulmonary arteriography showing various filling defects, with exclusion of the left lung and of various segments in the right lower lobe, consistent with chronic thromboembolic pulmonary hypertension.

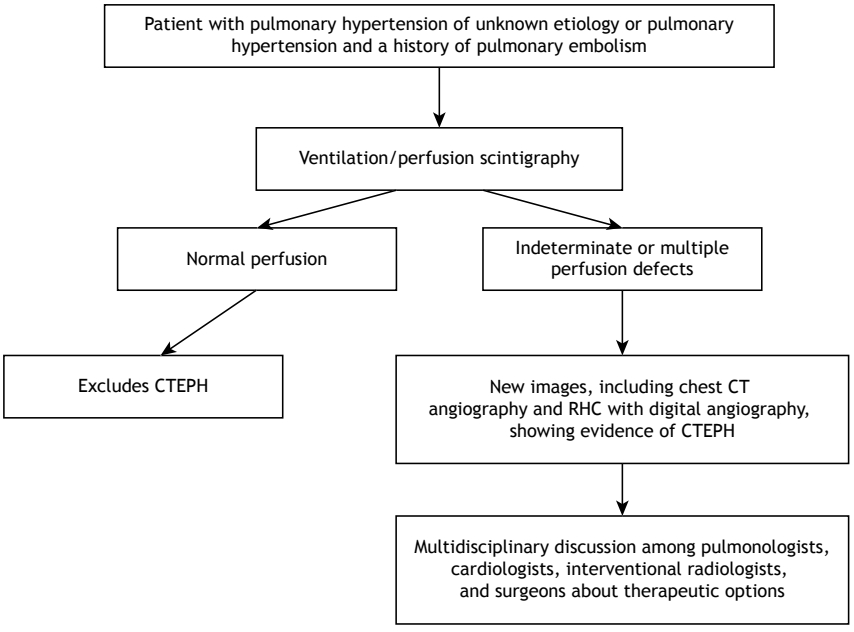

Figure 5. Investigation algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). RHC: right heart catheterization.

training programs can improve patient functional capacity; however, such programs should be started only after the use of specific treatments and under the supervision of teams with experience in caring for patients with PH; 3) immunization against influenza and pneumococcal infection should be performed during outpatient follow-up; 4) psychological and social support is desirable; 5) patients should be

advised of the risks of elective surgery and long air travel; 6) diuretics should be used in the presence of circulatory congestion associated with right ventricular failure; 7) the criteria for recommending home oxygen therapy are the same as those in patients with COPD, although there is no specific evidence for its use; and 8) it should be emphasized that there is no indication for the use of calcium channel blockers in CTEPH patients.

Anticoagulation

All patients with CTEPH should receive full anticoagulation indefinitely as from the time of diagnostic suspicion. Confirmation of the diagnosis should be made only after at least three months of anticoagulation so that any reversible vascular effect produced by anticoagulation will have occurred (i.e., so that any possible acute residual component will have been neutralized).[10] Anticoagulation should be continued also in the postoperative period if the patient undergoes PTEA, regardless of surgical success, and during clinical treatment of non-operated patients.[1]

The choice of an optimal anticoagulant for the treatment of CTEPH is still a subject of controversy in the literature. Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) can be used. Traditionally, as well as in the major articles in the literature, VKAs are the most widely used, with a therapeutic target international normalized ratio between 2.0 and 3.0.[1,18] Despite the lack of specific studies about CTEPH, DOACs have been rapidly incorporated into the treatment of CTEPH worldwide because of their convenient dosing schedules, stable pharmacokinetic properties, safety profile in terms of major bleeding, and good results, as well as their good acceptance in the context of acute PTE.[44] In 2016 in Germany, 51.0% and 46.2% of 392 patients diagnosed with CTEPH received anticoagulation with DOACs and VKAs, respectively.[45] In Brazil, a case series of patients with CTEPH showed that the use of DOACs in this situation was safe and efficient, regardless of the surgical status of the patients.[46] However, a study conducted in the UK suggests caution in the use of DOACs in CTEPH.[47] In that multicenter, retrospective study, 794 and 206 patients were treated with VKAs and DOACs, respectively, after PTEA. There were no differences in improvement in hemodynamics or functional status after surgery between the two groups, nor were there differences in major bleeding over a follow-up of 612 ± 702 days (0.7% per person/year). However, venous thromboembolism recurrence was higher in those treated with DOACs than in those treated with VKAs (4.62% vs. 0.76% per person/year; p = 0.008), with no differences in survival. Definitive conclusions about the role of DOACs in CTEPH still require further evidence from prospective studies or data from large registries. Therefore, the use of DOACs as the drugs of choice for patients with CTEPH still cannot be recommended. In addition, it is worthy of note that the use of DOACs in patients with antiphospholipid syndrome is not recommended to date because some studies have reported an increased rate of thromboembolic events in the group treated with DOACs when compared with the group treated with VKAs.[48,49]

Surgical treatment: PTEA

The presence of fibrous material obstructing the vascular lumen (Figure 6) shows why PTEA is the treatment of choice for patients with CTEPH.[2] The surgical results are excellent, depending on the level of experience of the referral center, as well as on appropriate patient selection.[50] Patients with CTEPH who undergo PTEA have a better prognosis than do non-operated patients, even when we consider that up to half of the operated patients may still have some degree of PH after the surgical procedure.[51] It is important not to confuse PTEA with embolectomy, which consists in removing only acute (nonendothelialized) thrombi and is used as reperfusion therapy in acute PTE.

Referral centers

Facilities that have adequate infrastructure to perform PTEA and BPA and have a multidisciplinary team with clinicians, surgeons, radiologists, and intensivists, are considered referral centers for CTEPH.[51] The team should be experienced in the management of this condition, should be prepared for the perioperative management of patients with CTEPH, and should perform at least 10 PTEAs per year.[50] Less-experienced centers, which perform fewer than 10 PTEAs per year, reported higher mortality rates than did centers that perform more than 50 PTEAs per year (8.8% and 3.4%, respectively). Ideally, referral centers for CTEPH should strive for excellence, performing more than 20 PTEAs per year, with mortality rates < 10%.[52]

Patient selection

Patient selection considers the amount of surgically accessible thromboembolic material, as well as its effects on pulmonary vascular resistance (PVR), in order to determine the potential hemodynamic improvement that may result from the surgical intervention.[51] The concept of proportionality between the extent of obstruction and the hemodynamic presentation is somewhat subjective and is related to the level of experience of the center. In certain situations, getting a second opinion from experienced centers regarding operability might be useful for novice centers. In a study that evaluated pharmacological interventions in patients with CTEPH, in which assessment of operability was confirmed or not by centers with wide experience in the surgical management of CTEPH, 69 (22%) of 312 patients who were initially regarded as technically inoperable were reclassified as viable candidates for PTEA,[53] clearly demonstrating the role that the learning curve plays in the decision making of whether or not to recommend the surgical intervention and justifying the requirement that, in

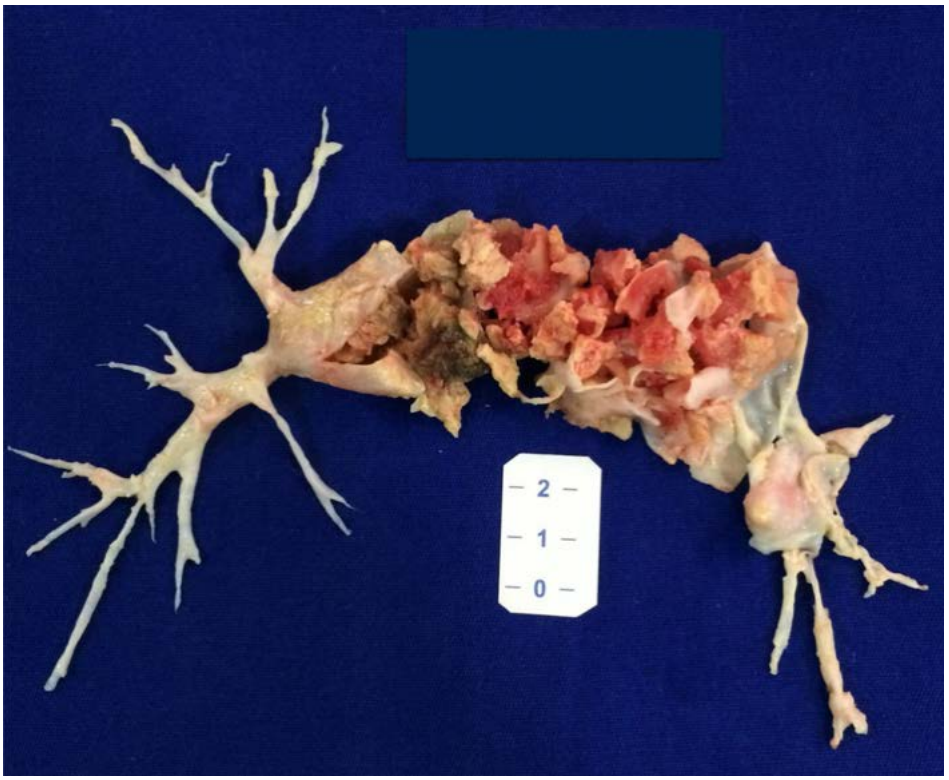

Figure 6. Surgical specimen obtained during pulmonary thromboendarterectomy.

order for a center to be classified as a referral center, it should perform a minimum number of PTEAs. ·In the decision making of whether or not to recommend PTEA, factors associated with favorable surgical results should be considered, such as a history of deep vein thrombosis/PTE, absence of comorbidities, absence of signs of right heart failure, functional class II or III status, clear proportionality between the imaging abnormalities and the hemodynamic data, bilateral lower lobe disease, PVR less than 1,000 dyn · s · cm^{-5}, and high pulse pressure.[1] The absence of these characteristics does not contraindicate PTEA, but indicates higher surgical risk, and should therefore be weighed against the level of experience of the center in performing the surgical procedure.

A specific population to be considered to be selected for PTEA is that of patients with unilateral occlusion of one of the main branches of the pulmonary artery, also known as complete pulmonary vascular exclusion (see Figure 4, left lung). In such cases, although the patients are usually younger and have lower pulmonary artery pressure and lower PVR, local factors can make it difficult to perform PTEA and can compromise the surgical result. It is not uncommon, in cases of complete unilateral pulmonary vascular exclusion, that the arterial bed distal to the obstruction shows severe postobstructive arteriopathy or remains hypoplastic, causing inadequate reperfusion despite PTEA.[54] Therefore, cases of unilateral pulmonary artery occlusion should be considered a priority for PTEA, which should be performed before the development of a postobstructive arteriopathy.[55]

Given the low rates of venous thromboembolism in the postoperative period after PTEA, most centers of excellence have abandoned the practice of inserting an inferior vena cava filter prior to surgery. The recommendation is to restart anticoagulation as early as possible, taking into account perioperative bleeding status and the presence of a coagulopathy, as well as the presence of other comorbidities.

Surgical procedure

PTEA is performed through a longitudinal median sternotomy using cardiopulmonary bypass (CPB), with the patient being cooled to 18-20°C. This is followed by a period of total circulatory arrest (TCA) of up to 20 min, during which either the right or the left pulmonary artery is approached (Figure 7) and the obstructive fibrous material is removed. Next, CPB is resumed, and blood is recirculated for 10 min, after which there is one more cycle of TCA for the contralateral approach.[56] In most cases, two periods of TCA are sufficient, one for each side approached, but, if necessary, more periods of TCA can be performed until the pulmonary arteries are completely unblocked. After the last period of TCA, CPB is resumed and the patient is slowly rewarmed, at which point other interventions can be made, such as coronary artery revascularization or correction of congenital malformations. Given the need for long CPB time with periods of TCA, measures such as protection

of the brain by local cooling and assessment of brain activity should be implemented to minimize adverse effects. In addition, anesthetic care, perioperative mechanical ventilation strategies, anticoagulation management, and adequate hemodynamic monitoring are of vital importance, as are anesthesiologists and intensivists trained in performing this type of surgery and in providing extracorporeal membrane oxygenation (ECMO), if necessary.[57] Despite the extent of the surgical procedure, the European registry shows that operated patients have significantly greater survival than non-operated patients, underscoring the role of PTEA as the first-line treatment for eligible patients.[50] On the basis of intraoperative findings, patients are classified into resection categories, which are associated with surgical benefit and long-term prognosis (Chart 4).[55]

The major complications of PTEA are hemodynamic and respiratory. Right ventricular dysfunction in the immediate postoperative period can make it difficult to discontinue CPB. Venoarterial ECMO, although rarely necessary, can provide a bridge to right ventricular recovery.[58] Another complication is residual PH, which occurs in up to 50% of the patients, although a recent meta-analysis involving 4,868 patients reported its presence in approximately 25% of the operated patients.[59] Pulmonary reperfusion injury is a severe respiratory complication that occurs most frequently in the first 48 h after surgery and can cause inflammatory pulmonary edema and severe hypoxemia. In some cases, venovenous ECMO may be necessary for ventilatory support.[57]

The impact of PTEA on the right ventricle suggests the presence of reverse remodeling,[60] with a reduction in ventricular volumes and mass, as well as an improvement in ventricular ejection fraction. Moderate to severe tricuspid insufficiency is common in patients with CTEPH but in general does not need to be corrected during PTEA, given the reduction in right ventricular dimensions after the reduction in PVR.[55] Bilateral lung transplantation (exceptionally heart-lung transplantation) is the surgical treatment for patients with PH refractory to other therapies who have no contraindications to this procedure. Patients with CTEPH rarely undergo lung transplantation, since they respond significantly to other therapies.[61]

BPA

For patients with CTEPH who have residual PH (after surgery) or for whom surgery is not feasible

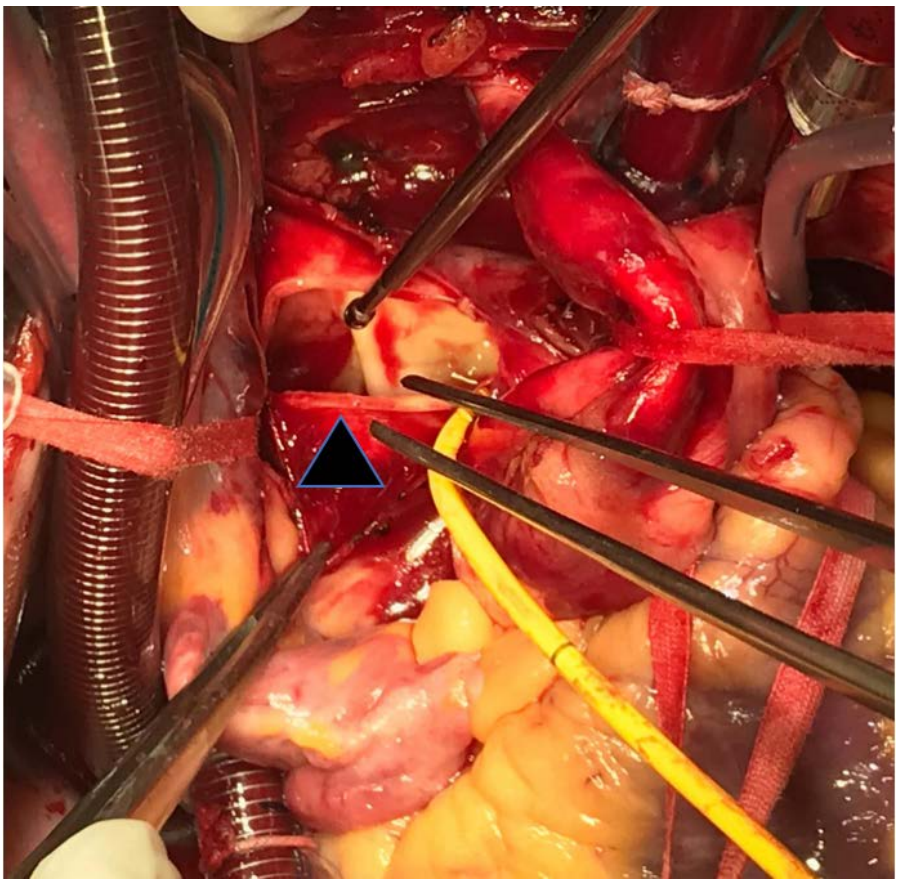

Figure 7. Image of the surgical field of a patient undergoing pulmonary thromboendarterectomy. The pulmonary artery is sectioned longitudinally (arrowhead); an organized white thrombus can be seen within the pulmonary artery, adjacent to the dissecting clamps. There is no blood flow through the pulmonary artery, given that the patient is on cardiopulmonary bypass during a period of total circulatory arrest (cannulas on the left).

(for technical reasons or because of thrombus inaccessibility), treatment options used to be limited to clinical treatment or pulmonary transplantation.[1,55] However, since the late 1990s, reports of pulmonary artery catheterization procedures for dilation of chronically obstructed branches have been published.[62] BPA, or simply pulmonary angioplasty, is currently an important resource for the treatment of patients with CTEPH.[1,63,64]

BPA consists in the insertion a balloon-tipped catheter that can be used to dilate systemic arteries (e.g., femoral, renal, or even coronary arteries) and the subsequent inflation of the balloon within the chosen vessel, without the need for prostheses, such as stents (Figure 8), or the use of thrombolytics or thrombus fragmentation techniques, as can occur in acute PTE. The balloon is inflated to generate enough pressure to disrupt the fibrin network or displace it radially, producing an improvement in local blood flow and an increase in the diameter of the treated vessel, thus leading to a reduction in PVR.[65-68]

Because the disease is rarely limited to a single area, this treatment is repeated approximately 6-8 times (sessions) for each patient, since approaching more than 4 segments in the same session increases the risk of complications, such as reperfusion edema or rupture of vessels (causing alveolar hemorrhage). From the first reports to more consistent studies,[65,67,68] BPA has gradually been incorporated into the treatment algorithm for CTEPH, because the results of this intervention have shown that it can improve hemodynamics, improve symptoms, and increase exercise capacity and right ventricular function, with significantly reduced rates of complications.[63,69,70] Retrospective studies have shown that the benefits of BPA also persist in the medium term,[71,72] and study groups outside Japan were able to reproduce encouraging results.[64,73] A meta-analysis of 12 observational studies (a total of 493 patients) reported a 2-year mortality rate of 1.3% in patients who underwent BPA, a rate that is significantly lower than that associated with the pharmacological treatment alone.[74] The role of BPA in patients with surgically resectable lesions but for whom surgery is contraindicated because of comorbidities or who refuse surgery has yet to be established.[1] BPA, as well as PTEA, should be performed at referral centers by professionals trained in the procedure.

Pharmacological treatment

Technically inoperable CTEPH

All patients with CTEPH should be assessed for eligibility for PTEA at a referral center, as defined previously, because PTEA is potentially curative. However, given that not all patients are eligible for PTEA, either because of the presence of inaccessible thrombi or because PVR is disproportionately high for the degree of vascular obstruction seen on imaging studies,[50] pharmacological treatment, such as BPA, is an alternative.

Three randomized, placebo-controlled clinical trials (Table 2) reported the benefits of using PAH-specific medications in patients with CTEPH who are inoperable (functional class II-IV).[75-77] The medications evaluated

Chart 4. Surgical classification of chronic thromboembolic pulmonary hypertension.

Surgical level	Location of thromboembolism
Level 0	No evidence of CTE in either lung
Level I	CTE starting in the main pulmonary arteries
Level IC	Complete occlusion of one main pulmonary artery with CTE
Level II	CTE starting at the level of lobar arteries or in the descending pulmonary artery
Level III	CTE starting at the level of segmental arteries
Level IV	CTE starting at the level of subsegmental arteries

Adapted from Galiè et al.[52] CTE: chronic thromboembolism.

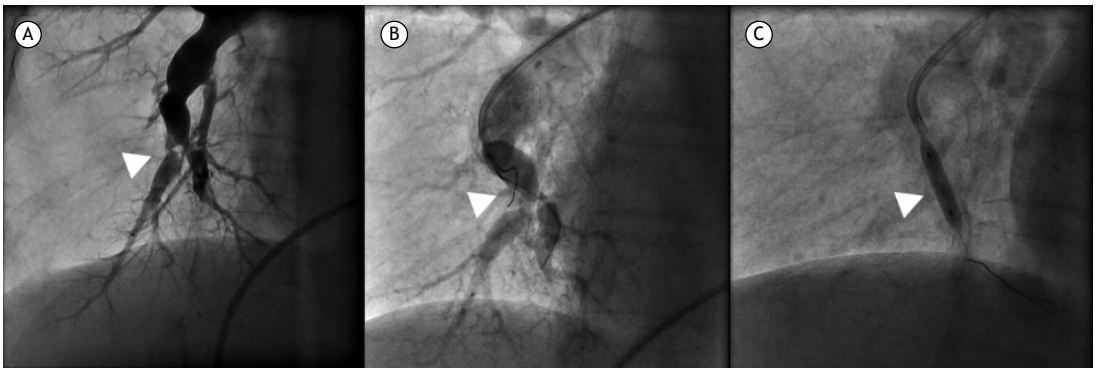

Figure 8. Pulmonary artery angioplasty. In A, multiple circumferential lesions in a segmental branch of the right pulmonary artery; in B, passage of a guidewire; and, in C, passage and inflation of a balloon to dilate the vascular lumen and reduce pulmonary vascular resistance.

were bosentan,[75] riociguat,[76] and macitentan.[77] Those trials showed different clinical endpoints. In the trial regarding bosentan,[75] the primary endpoint was a composite of an increase in six-minute walk distance (6MWD) and a reduction in PVR, whereas in the trial regarding riociguate,[76] it was an increase in 6MWD. In the trial regarding macitentan,[77] the primary endpoint was a reduction in PVR. In addition, two of the trials were phase III trials,[75,76] whereas one was a phase II trial.[77] The trials regarding riociguat and macitentan[76,77] showed positive outcomes, whereas that regarding bosentan,[75] which had a composite primary endpoint, the results cannot be considered positive because it showed an effect only in reducing PVR.

A meta-analysis involving 6 studies and 565 patients with CTEPH showed that the use of PAH-targeted drugs in this population led to a significant hemodynamic improvement, as well as to an improvement in symptoms, functional class, and exercise capacity. No differences were found in mortality or in the incidence of severe adverse events.[78]

Residual PH

Although PTEA can be curative, recent data suggest that approximately 25% of the operated patients have some degree of residual PH.[59] Some doubt exists regarding cutoff values for defining residual PH after PTEA. Whereas prospective studies have used the traditional cutoff value of 25 mmHg for defining it,[76] a cohort study of 880 patients who had been operated on at one of eight centers in the United Kingdom reported that a postoperative mPAP of 38 mmHg and postoperative PVR > 425 dyn · s · cm^{-5} correlated with a worse prognosis.[12] Currently, it is recommended that an mPAP value of 30 mmHg, invasively determined 3-6 months after PTEA,[79] be used to define the presence of significant residual PH. This value comes from the data analysis carried out in that cohort study,[12] which showed that an mPAP > 30 mmHg in the postoperative period after PTEA was associated with higher long-term mortality. The aforementioned trials[75,76] included patients with residual PH, defined as an mPAP ≥ 25 mmHg and PVR ≥ 300 dyn · s · cm^{-5}, more than six months after PTEA. In the trial regarding bosentan,[75] a reduction in PVR was observed also in the patients with residual PH, but there was no improvement in exercise capacity. In that regarding riociguat,[76] there was an improvement in 6MWD and a reduction in PVR also in the subgroup of patients who had previously been operated on. Macitentan was not evaluated in patients with residual PH.[77] Currently, riociguat is the only medication that has been approved by the American, European, and Brazilian regulatory agencies for the treatment of technically inoperable CTEPH or residual PH.

Combined pharmacological treatment

Regarding the macitentan trial,[77] 61% of the patients had already been treated with a phosphodiesterase-5 inhibitor and/or an oral or inhaled prostacyclin when they were started on either macitentan or placebo. The efficacy of macitentan was similar between those who had previously been treated and those who had not.[77] Other combinations of PH-targeted drugs have not been prospectively studied in CTEPH. The combination of riociguat and a phosphodiesterase-5 inhibitor is contraindicated; a study of one such combination reported a lack of benefit and a high rate of discontinuation due to systemic arterial hypotension in patients with PAH.[80]

Table 2. Randomized, double-blind, placebo-controlled clinical trials of drugs for the treatment of technically inoperable chronic thromboembolic pulmonary hypertension.[a]

Study	Jaïs et al.[75],[b]	Ghofrani et al.[76],[b]	Ghofrani et al.[77]
Drug	Bosentan	Riociguat	Macitentan
Dosing schedule	125 mg p.o., bid	0.5-2.5 mg p.o., tid	10 mg/day p.o., qd
Number of patients	157	261	80
Duration, weeks	16	16	16 and 24[c]
Residual or recurrent PH	41 (29.9%)	72 (27.6%)	–
Previous use of PH-specific medication	-	-	49 (61.3%)
Baseline 6MWD, m	342 ± 84	347 ± 80	352 ± 81
Effect on 6MWD, m	+2	+46	+34
Baseline PVR, dyn · s · cm^{-5}	783 (95% CI: 703-861)	787 ± 422	957 ± 435
Effect on PVR, %	−24	−31	−16
Major adverse effects[d]	Peripheral edema (13% vs. 7.5%) Hepatotoxicity (7.8% vs. 1.3%)	Headache (25% vs. 14%) Hypotension (9% vs. 3%)	Peripheral edema (23% vs. 10%) ↓ hemoglobin (15% vs. 0)

bid: twice a day; tid: three times a day; qd: every day; PH: pulmonary hypertension; 6MWD: six-minute walk distance; and PVR: pulmonary vascular resistance. [a]Values expressed as n or as mean ± SD. [b]We also included patients with residual PH after pulmonary thromboendarterectomy. [c]PVR at week 16 and 6MWD at week 24. [d]Drug versus placebo.

PH medications as "bridging to surgery"

The evidence supporting pharmacological treatment as bridging to surgery is scarce. International registry data have shown delayed referral to surgery and worse outcomes in those patients treated prior to referral.[50,81] Recently, a case series has demonstrated some benefit of using pharmacological therapy as bridging to surgery in a population with more severe hemodynamic impairment.[82] Nevertheless, clinical treatment for improving the hemodynamic status of patients prior to the surgical procedure is not recommended as part of the routine treatment of CTEPH. Clinical treatment can be considered in selected cases only at referral centers with wide experience in the surgical treatment of patients with CTEPH, so that it will not lead to a delay in accessing the treatment of choice.

Patients either not eligible for surgery because of comorbidities or who refuse surgery

Patients with accessible thrombi but who were either not eligible for surgery because of comorbidities or refused to undergo surgery were not included in the studies presented above; such patients require an individualized approach.

Pharmacological treatment or angioplasty

One study included 105 patients with CTEPH not undergoing PTEA who were randomized either to receive riociguat or to undergo BPA in one of 14 centers in France.[83] In that study, the efficacy of BPA was greater, given that it reduced PVR by 60%, compared with 32% for riociguat ($p < 0.0001$). In addition, the proportion of patients who improved at least one functional class was higher among those undergoing BPA than among those treated with riociguat (88% vs. 49%; $p < 0.0001$). The reduction in brain natriuretic peptide levels was also 67% higher in the BPA group than in the riociguate group ($p < 0.0001$). There was no difference in 6MWD between the groups. The benefits of BPA came at a price. The proportion of patients with at least one adverse event was higher among those undergoing BPA than among those treated with riociguat (50% vs. 26%), as was the proportion of patients with at least one severe adverse event directly related to treatment (14% vs. 9%). None of the patients discontinued treatment because of adverse events, and there were no deaths during the 26 weeks of the study. These data suggest that BPA should be tried before pharmacological treatment with riociguat in patients with CTEPH who are not eligible for surgery. If BPA is not completely successful in normalizing the patient's pressure, pharmacological treatment with riociguat would then be indicated.[1] It should be emphasized, however, that that study[83] was the first to propose such an approach and that the long-term results of BPA as an initial treatment option if PTEA is not possible—results that would define the role of BPA in this setting—remain unknown. Nevertheless, this treatment option can be accepted as a possibility for patients who are not candidates for surgery. If BPA is not readily available, it is advisable to start pharmacological therapy so that there is no delay in initiating treatment.

Multimodal treatment

The combination of different therapeutic modalities is already a reality in CTEPH. There are reports and case series on different combinations of therapeutic strategies, such as PTEA plus pre- and/or post-operative drugs, BPA plus drugs, and, more recently, the combination of PTEA, BPA, and drugs. This last combination is still an individualized approach and depends on the location of the obstruction, the severity of hemodynamic impairment, and the expertise of the team.[84] Ongoing long-term prospective studies may clarify the role of combined methods in the treatment of CTEPH, as well as the indications and the appropriate timing for each intervention.

The algorithm proposed for the therapeutic approach to CTEPH is described in Figure 9.

Follow-up

Patients with CTEPH, whether they undergo PTEA or not, should be evaluated at least every 3-6 months. The factors assessed include clinical variables (functional class, symptom progression, signs of right heart failure); biochemical markers (natriuretic peptides); cardiac echocardiography and/or cardiac MRI (right ventricular function by tricuspid annular plane systolic excursion [TAPSE] or ejection fraction, atrial dilatation, presence of pericardial effusion); exercise testing (either 6MWD or oxygen consumption and ventilatory equivalent during CPET); and hemodynamic variables (right atrial pressure, cardiac index, and mixed venous oxygen saturation). At each visit, patient risk should be stratified on the basis of these variables.[85] There are some risk stratification models that were initially used in PAH and have currently been validated in CTEPH,[86,87] and the therapeutic target is to maintain patients in the low-risk category all the time (Table 3), with an increase in quality of life.[88] CPET can also be used in the assessment of the severity of CTEPH and in the follow-up of patients with CTEPH, but therapeutic target thresholds have yet to be defined for this population.

Screening for CTEPH after acute PTE

All patients who had acute PTE should be clinically evaluated at 3-6 months of follow-up. At follow-up visits, in addition to the assessment of symptoms, attention should be paid to risk factors that are present and are predictors of an increased risk of CTEPH, such as recurrent venous thromboembolism, young age, unprovoked venous thromboembolism, extensive filling defects, signs of right ventricular dysfunction (e.g., pulmonary artery systolic pressure > 60 mmHg and/or right ventricular hypertrophy), and previous

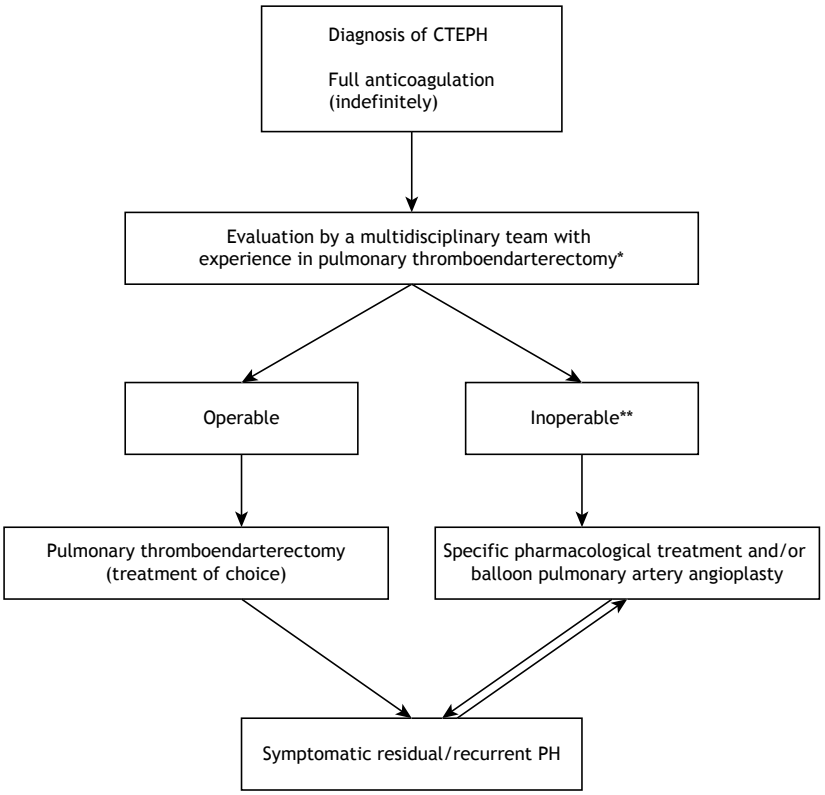

Figure 9. Treatment algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). PH: pulmonary hypertension. *Multidisciplinary team: a surgeon, a radiologist, and a clinician with experience in pulmonary hypertension. **Depending on the level of experience of the center, consider getting a second opinion from another team specializing in pulmonary thromboendarterectomy.

Table 3. Risk stratification.

Determinants of prognosis	Estimated one-year mortality		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right ventricular failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasionally[a]	Repeatedly[b]
WHO-FC	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
Plasma levels of NT-proBNP/ BNP	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging (ECHO, chest MRI)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamic parameters	RA pressure < 8 mmHg CI ≥ 2.5 L · min · m^2 SvO_2 > 65%	RA pressure 8-14 mmHg CI 2.0-2.4 L · min · m^2 SvO_2 60-65%	RA pressure > 14 mmHg CI < 2.0 L · min · m^2 SvO_2 < 60%

Adapted from Galiè et al.[2] WHO-FC: World Health Organization functional class; 6MWD: six-minute walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ECHO: echocardiography; MRI: magnetic resonance imaging; RA: right atrial; CI: cardiac index; and SvO_2: mixed venous oxygen saturation. [a]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient. [b]Repeated episodes of syncope, even with little or regular physical activity.

pulmonary artery CT angiography findings of CTEPH (see Chart 3).[36]

There is no recommendation that all survivors of acute PTE should be actively investigated.[89] However, patients with persistent or recurrent dyspnea or with limited exercise capacity three months after treatment of the acute event should be assessed for CTEPH. The initial test is echocardiography. If

Chart 5. Recommendations for the management of chronic thromboembolic pulmonary hypertension.

Diagnosis
• For a diagnosis of CTEPH, the following three diagnostic criteria must be met: at least three months of effective anticoagulation; invasive confirmation of pulmonary hypertension: mean pulmonary artery pressure > 20 mmHg; and confirmation of chronic thromboembolism by chest CT angiography, ventilation/perfusion lung scintigraphy, and/or pulmonary arteriography
• Every patient under investigation for pulmonary hypertension should be evaluated for the possibility of CTEPH via ventilation/perfusion lung scintigraphy
Screening
• There is no recommendation that all patients with PTE should be investigated for CTEPH
• Patients with a history of VTE (DVT or PTE) who, after 3-6 months of anticoagulation, present with dyspnea should be investigated for CTEPH
• Patients with a history of PTE and multiple risk factors for CTEPH, even if asymptomatic, can be investigated for CTEPH
• Echocardiography is the initial screening test for CTEPH
• In the presence of echocardiographic findings that are suggestive of pulmonary hypertension, the screening test for CTEPH is ventilation/perfusion lung scintigraphy
Treatment
• All patients with CTEPH should be maintained on full anticoagulation indefinitely
• All patients with CTEPH should be evaluated for pulmonary thromboendarterectomy at a referral center (see definition for referral center)
• It is suggested that less-experienced centers request a second opinion from a more experienced center before contraindicating the surgical procedure
• If surgery is contraindicated by an established referral center or by the presence of postoperative residual pulmonary hypertension (mean pulmonary artery pressure > 30 mmHg, measured 3-6 months after surgery), patients should undergo pharmacological treatment and/or balloon pulmonary angioplasty
• Supportive care, including diuretics and long-term home oxygen therapy, should be implemented on a case-by-case basis

CTEPH: chronic thromboembolic pulmonary hypertension; PTE: pulmonary thromboembolism; VTE: venous thromboembolism; and DVT: deep vein thrombosis.

there are findings indicating intermediate or high likelihood of PH, ventilation/perfusion lung scintigraphy should be performed. In cases with a low likelihood of PH, additional factors should be observed, such as natriuretic peptide levels, risk factors for CTEPH both during the acute event and within the context of the patient, and, eventually, CPET results. CPET is a maximal exercise test, the results of which may be suggestive of CTEPH, which would then indicate the need for further investigation with echocardiography and, subsequently, RHC.[90] In addition, CPET allows the identification of other mechanisms that cause dyspnea in this population of patients who do not have CTEPH.

There is as yet no defined approach to patients with pulmonary thromboembolic disease, that is, those with residual thrombi and no PH at rest. It is suggested that such patients also be referred to referral centers for an individualized approach.

FINAL CONSIDERATIONS

Chart 5 summarizes the recommendations for the management of CTEPH.

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