An expert opinion of the Polish Cardiac Society Working Group on Pulmonary Circulation on screening for chronic thromboembolic pulmonary hypertension patients after acute pulmonary embolism: Update

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DOI: 10.33963/KP.a2022.0141

Received:
June 6, 2022

Accepted:
June 6, 2022

Early publication date:
June 6, 2022

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism (APE). Both pharmacological and invasive treatments for CTEPH are available in Poland, and awareness of the disease among physicians is growing. It has been suggested that the COVID-19 pandemic may increase the incidence of CTEPH and facilitate disease detection during more advanced stages of the illness. Thus, the Polish Cardiac Society's Working Group on Pulmonary Circulation, in cooperation with independent experts in this field, launched the updated statement on the algorithm to guide a CTEPH diagnosis in patients with previous APE. CTEPH should be suspected in individuals after APE with dyspnea, despite at least 3 months of effective anticoagulation, particularly when specific risk factors are present. Echocardiography is the main screening tool for CTEPH. A diagnostic workup of patients with significant clinical suspicion of CTEPH and right ventricular overload evident on echocardiography should be performed in reference centers. Pulmonary scintigraphy is a safe and highly sensitive screening test for CTEPH. Computed tomography pulmonary angiography with precise detection of thromboembolic residues in the pulmonary circulation is important for the planning of a pulmonary thromboendarterectomy. Right heart catheterization definitively confirms the presence of pulmonary hypertension and direct pulmonary angiography allows for the identification of lesions suitable for thromboendarterectomy or balloon pulmonary angioplasty. In this document, we propose a diagnostic algorithm for patients with suspected CTEPH. With an individualized and sequential diagnostic strategy, each patient can be provided with suitable and tailored therapy provided by a dedicated CTEPH Heart Team.

Key words: chronic thromboembolic pulmonary hypertension, acute pulmonary embolism, echocardiography, diagnostic algorithm, computed tomography pulmonary angiography

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) has been an area of particular interest to researchers and specialists in pulmonary circulation disorders in recent years. One important problem is the need for the early diagnosis of CTEPH, both in patients with and without a history of acute pulmonary thromboembolism (APE).

Indeed, the pathogenic mechanism of CTEPH is not limited to mechanical occlusion of a portion of the pulmonary arterial bed by unrecognized organized thromboembolic lesions. Redistribution of blood flow to the obstructed portion of the pulmonary artery bed, as well as feeding it from high-pressure systemic arterioles (especially bronchial arterioles), further leads to progressive, adverse, and irreversible remodeling of pulmonary arterioles and small pulmonary veins, which progressively increases right ventricular overload.

An early diagnosis of CTEPH would allow for the implementation of therapy before the development of these changes in the pulmonary microcirculation, improving the effectiveness of treatment and the long-term prognosis for patients.

The purpose of this article, developed by a team of experts from the Polish Cardiac Society Working Group on Pulmonary Circulation, is to give an update on clinical strategies aimed at promoting an early diagnosis of CTEPH in patients with a history of APE. This is a challenging task for a number of reasons. Although many patients report impaired exercise tolerance after an episode of APE, in the vast majority of cases, this is not associated with resting pulmonary hypertension (PH). It also does not occur in many individuals despite the presence of residual intravascular lesions after APE. On the one hand, exertional dyspnea persisting after APE and even echocardiographic features of right ventricular overload result more often from chronic obstructive pulmonary disease (COPD) or left ventricular dysfunction than from possible residual post-embolic effects. On the other hand, the absence of spontaneously reported symptoms after APE does not rule out CTEPH, especially if the patient restricts their activity believing that they should do so after a severe, life-threatening disease, as they were informed at the time of the diagnosis of APE.

The current 2019 European Society of Cardiology (ESC) guidelines on APE, as well as the document developed by the experts from the European Respiratory Society (ERS), which relate to chronic thromboembolic pulmonary disease (CTEPD), provide guidelines for the early detection, but also exclusion, of sequelae relating to APE which require specific treatment [1, 2].

We consider it particularly important to organize and present this guidance for national use during a period of a rapid increase in pulmonary thromboembolic complications associated with the COVID-19 pandemic. It cannot be ruled out that the health impact of COVID-19 will include an increase in the frequency of CTEPD as well as CTEPH in the months and years to come.

CTEPH EVALUATION IN PATIENTS WITH A HISTORY OF APE: CLINICAL CONSIDERATIONS

More than 70% of patients with confirmed CTEPH have previously experienced at least one episode of APE. In the Polish registry, 83% of patients developed CTEPH after the initial thromboembolic event [1, 3]. There is a growing body of data indicating that, despite complete anticoagulation treatment for at least 3 months, approximately 50% of patients with a history of APE report a persistent decline in physical performance compared to the pre-disease state [4–6]. Recently, the term "post-APE syndrome" has been introduced to include CTEPH, CTEPD, deconditioning, and psychological problems caused by APE [4–6]. Although persistent dyspnea may be caused by other chronic pulmonary and cardiac conditions, the main diagnostic goal of post-APE syndrome is to exclude CTEPH since diagnostic delays significantly worsen patient prognosis and outcomes [7].

In early CTEPH, clinical symptoms are very uncharacteristic, with exertional dyspnea being the most common. Symptoms of right heart failure only appear in advanced forms of the disease. The uncharacteristic clinical picture makes the average time from the onset of CTEPH symptoms to diagnosis >1 year, confirming the low awareness of this disease among healthcare providers [1, 8, 9].

The absence of a history of APE does not exclude a diagnosis of CTEPH. However, patients who had an APE are at a higher risk of developing CTEPH. It is noteworthy that some patients already have features of CTEPH at the time of diagnosis, e.g., an elevated tricuspid regurgitant peak gradient >50 mm Hg on echocardiography [10].

A tricuspid regurgitant peak gradient >50–60 mm Hg and/or other features of significant right ventricular overload are indicative of a chronic thromboembolic process or other concurrent chronic pulmonary or cardiac diseases. Analysis of computed tomography pulmonary angiography (CTPA) images from the acute period of APE is also important. Table 1 shows the radiological features indicative of the chronic component of the disease [1].

In the evaluation of CTPA scans obtained from 341 patients with APE, 22% showed at least one of the following features suggestive of chronic disease: pulmonary trunk dilatation, pulmonary artery stenosis, presence of linear filling defects in the vessel lumen, bronchial artery dilatation, features of right ventricular wall hypertrophy, or flattening of the interventricular septum. At 2-year follow-up, nine (2.6%) patients developed CTEPH. Importantly, the presence of at least one of these characteristics increased the likelihood of developing CTEPH almost 8-fold [9].

The current ESC guidelines for the management of APE do not recommend routine testing for CTEPH in all patients after an episode of disease. However, CTEPH should be suspected in patients with the post-APE syndrome who, despite at least 3 months of effective anticoagulation treatment, have persistent exertional dyspnea or reduced

Table 1. Abnormalities found on CTPA suggestive of CTEPH in patients with APE

Abnormalities indicative of pre-existing thromboembolic pulmonary hypertension as detected by CTPA. Based on the ESC 2019 guidelines [1]
Direct vascular signs
Eccentric wall-adherent filling defect(s), which may calcify
Abrupt tapering and truncation
Complete occlusion and pouch defects
Intimal irregularity
Linear intraluminal filling defects (intravascular webs and bands)
Stenosis and post-stenotic dilatation
Vascular tortuosity
Indirect vascular symptoms
Significant right ventricular hypertrophy, right atrial dilatation
Pericardial effusion
Pulmonary artery dilatation (>29 mm in men and >27 mm in women) and/or pulmonary artery calcification
Systemic collateral arterial supply (bronchial arterial collaterals towards pulmonary post-obstructive vessels)
Pulmonary parenchymal lesions
Mosaic attenuation of the lung parenchyma resulting in geographical variation in perfusion

Abbreviations: APE, acute pulmonary embolism; CTPA, computed tomography pulmonary angiography; CTEPH, chronic thromboembolic pulmonary hypertension; ESC, European Society of Cardiology

Table 2. Factors that increase the risk of CTEPH after APE

Factors that increase the risk of CTEPH after APE
Symptoms of APE lasting more than 2 weeks before diagnosis
Large number of thrombi in the pulmonary arteries during APE
Previous episodes of PE or DVT
Echocardiographic signs of PH/RV dysfunction; RV/LV>1 (echocardiography or CTPA)
Significantly elevated tricuspid regurgitant peak gradient > 50 mm Hg in acute PE
Predisposing conditions: chronic inflammatory diseases (chronic osteoarthritis and chronic inflammatory bowel disease), status post-splenectomy, ventriculoperitoneal valve for hydrocephalus treatment, infected chronic i.v. lines or pacemakers, "non-0" blood type, substitution-treated hypothyroidism, thrombophilia (especially antiphospholipid syndrome and increased factor VIII activity), active cancer

Abbreviations: DVT, deep venous thrombosis; LV, left ventricle; PE, pulmonary embolism; PH, pulmonary hypertension; RV, right ventricle, other — see Table 1

physical capacity compared to the period before the acute episode of disease. Factors that increase the likelihood of developing CTEPH have been identified among individuals with a history of APE [1], as summarized in Table 2. Testing for CTEPH may be considered in patients with at least one of these risk factors.

We suggest that suspicion of CTEPH should be considered and diagnostic echocardiography should be initiated in all patients with persistent dyspnea or limitation of physical function of unclear cause despite 3 months of anticoagulation after an episode of APE, especially in the presence of the coexisting risk factors listed in Table 2 or the presence of changes on CTPA scan indicating a chronic character of the disease.

In addition, if a tricuspid regurgitant peak gradient >50–60 mm Hg is found in patients with APE, a follow-up echocardiogram after at least 3 months of anticoagulant therapy is indicated, regardless of the persistence of clinical symptoms.

NON-INVASIVE ASSESSMENT OF THE PULMONARY CIRCULATION IN PATIENTS WITH A HISTORY OF APE

Transthoracic echocardiography

Despite the dynamic development of imaging modalities, transthoracic echocardiography (TTE) is still the preferred screening test for CTEPH. TTE should be performed in any patient with dyspnea of unclear cause after a history of APE and at least 3 months of optimal antithrombotic therapy. TTE may also be considered in patients 3–6 months after an APE when CTEPH risk factors are present or when abnormalities on CTPA performed during the acute phase of the disease suggest pre-existing chronic thromboembolic changes (Table 1). When the tricuspid regurgitation maximum velocity on transesophageal echocardiography (TEE) is >2.8 m/s, or when the velocity is ≤2.8 m/s, but with other echocardiographic features suggestive of PH, the patient should be referred for a reference healthcare center consultation or pulmonary scintigraphy. Echocardiography should also be performed to assess the morphology and function of the left atrium and left ventricle, as well as the mitral and aortic valves, bearing in mind that the most common cause of PH is left heart pathology. Echocardiographic parameters suggestive of PH proposed in the ESC recommendations for the diagnosis and treatment of PH [1] are shown in Table 3.

Lung scintigraphy

In cases where there is clinical suspicion of CTEPH and echocardiographic features suggestive of PH are present, ventilation-perfusion lung scintigraphy is indicated. A normal scintigraphy result allows for the definitive exclusion of CTEPH. The typical ventilation-perfusion scintigraphy findings in patients with CTEPH are segmental or lobar perfusion defects. Scintigraphy allows for the differentiation between CTEPH and pulmonary arterial hypertension (PAH): the latter is typically associated with normal findings although subsegmental perfusion abnormalities may be present. Performing ventilation scans is intended to increase the specificity of the test, but it is acceptable to compare the perfusion scintigraphy result with a chest radiograph or computed tomography (CT) scan. Patients with CTEPH show normal ventilation or normal pulmonary parenchyma in areas of hypoperfusion.

Lung scintigraphy remains an important test when CTEPH is suspected, with a sensitivity and specificity of 96%–97% and 90%–95%, respectively, for the diagnosis of CTEPH [11]. If the test result is inconclusive, further diagnostic tests should be performed. The sensitivity of the scintigraphic examination has been greatly increased by the introduction of single-photon emission computed tomography (SPECT) imaging; now, with the use

Table 3. Echocardiographic indices suggestive of pulmonary hypertension used to assess the likelihood of PH, assessed in conjunction with tricuspid regurgitation velocity measurement[a]

Ventricles	Pulmonary artery	Inferior vena cava / right atrium
Right ventricular/left ventricular basal diameter ratio >1.0	Right ventricular acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/ /or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	Right atrial area (end-systolic) >18 cm^2
	Pulmonary artery diameter >25 mm	

[a]At least two echocardiographic parameters in two different categories

of hybrid techniques, its specificity has also improved. SPECT primarily provides scintigraphic images with much better resolution, while the introduction of CT enables absorption correction and simultaneous imaging of the lung parenchyma, improving the specificity of the study. Indeed, ventilation/perfusion SPECT is fast becoming the preferred scintigraphic method for suspected CTEPH [2]. A list of laboratories performing scintigraphy can be found in the Supplementary material.

CT scan of the lungs

CTPA imaging of the pulmonary arteries combined with high-resolution imaging for the diagnosis of parenchymal lesions is an essential component of the diagnostic workup for CTEPH. However, it should be strongly emphasized that a normal CTPA result does not exclude CTEPH; thus, in the traditional diagnostic algorithm, this test is placed after lung scintigraphy. CTPA has a 94%–95% sensitivity and specificity for the diagnosis of CTEPH [12]. The location and morphology of thrombi visualized by CTPA provide important information used to plan the surgical treatment of CTEPH. In addition, CT scanning illustrates lung parenchymal disease that may account for symptoms suggestive of CTEPH [1].

We have an increasing amount of data on the utility of dual-source CT in the diagnosis of CTEPH. This method allows for better visualization of the subsegmental pulmonary arteries. Research is also underway aimed at examining the feasibility of using magnetic resonance imaging to diagnose patients with CTEPH.

INVASIVE ASSESSMENT OF THE PULMONARY CIRCULATION IN PATIENTS WITH A HISTORY OF APE

Right heart catheterization

Confirmation of PH requires invasive direct measurement of pulmonary artery pressure. The current ESC guidelines set the cut-off point for the diagnosis of PH at 20 mm Hg for mean pulmonary arterial pressure [13]. The definition of CTEPH also includes the condition of documenting a normal pulmonary artery wedge pressure ≤15 mm Hg. The ESC guidelines indicate that right heart catheterization should be performed in patients with suspected CTEPH based on symptoms, risk factors, and non-invasive tests, including echocardiography [1]. Additional indications for right heart catheterization (RHC) include eligibility for pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) and the inclusion of specific therapy targeting pulmonary arteries [14]. RHC is a relatively safe procedure; however, even in experienced centers, the risk of fatal complications is anticipated at about 0.05% [15]. Exercise RHC should be considered when CTEPD is suspected, which is characterized by normal resting pulmonary pressure and pulmonary resistance values, and their abnormal increase during exercise. An exercise-induced increase in the slope of the mean pulmonary arterial pressure to cardiac output (mPAP/CO curve >3 mm Hg/l/min) due to persistent embolic material in the pulmonary bed is considered abnormal.

Pulmonary arterial angiography

Pulmonary arterial angiography is still considered the "gold standard" for the diagnosis of CTEPD and CTEPH. It is a basic diagnostic tool used during the qualification of the patient for an appropriate method of surgical treatment. Pulmonary angiography should be performed via the selective injection of contrast medium into the pulmonary arteries. The vasculature of each lung should be imaged during stopped breathing in at least two images e.g., posterior-anterior and lateral. The use of digital subtractive angiography, biplane cameras, and 3D rotational angiography allows clinicians to reduce the volume of the contrast agent used and to better visualize the subsegmental arteries. The technical principles of performing pulmonary arteriography have been described in detail elsewhere [14]. Analysis of angiographic images requires experience and knowledge of the anatomy of the pulmonary circulation. We evaluate the location, extent, and morphology of chronic thromboembolic lesions, which are different from the thrombi found in APE. The assessment of peripheral pulmonary parenchymal perfusion is important.

Coronary angiography should be considered in patients older than 55 years who are eligible for surgical treatment of CTEPH. Currently, routine implantation of venous filters before PEA is not recommended.

DIAGNOSTIC STRATEGY IN SUSPECTED CTEPH AND DIAGNOSTIC ALGORITHM

TTE is recommended if CTEPH is clinically suspected (i.e., dyspnea, worsening of exercise tolerance compared to the period before the episode of APE, etc.) in a patient with a history of APE and at least 3 months of effective antithrombotic therapy. TTE may also be considered in patients 3–6 months post-APE who have risk factors for CTEPH or have lesions suggestive of CTEPH in acute phase CTPA. In special cases involving patients with symptoms of severe right ventricular failure and severe PH who do not improve after initial treatment of APE, eligibility for invasive treatment may be considered earlier than 3 months. However, when a patient with a history of APE reports shortness of breath many months earlier, the first step should be to exclude another episode of APE and consider other causes of dyspnea. If CTEPH is likely, a TTE should be performed to confirm suspected features of right ventricular overload.

If an intermediate or high probability of PH is found on TTE, pulmonary scintigraphy should be performed, or if the test is difficult to access, the patient should be referred to a reference center. If this test is negative, CTEPH can be ruled out as the cause of the clinical and echocardiographic symptoms, and another cause should be sought. When perfusion impairment of at least one segment is found without associated parenchymal or ventilatory abnormalities, a diagnosis of CTEPH is likely. When the scintigraphy image is equivocal, the diagnosis of CTEPH is uncertain. In both of these situations, further diagnostic testing should be performed. CTPA is an imaging study of embolic changes in the pulmonary bed and should be performed when the diagnosis of CTEPH on pulmonary scintigraphy is uncertain or probable. Definitive confirmation of CTEPH is obtained by performing RHC, followed by pulmonary arteriography. If the patient had a CTPA at the time of the diagnosis of APE, a repeat test may be considered after a period of at least 3 months of anticoagulant treatment. The finding of post-thrombotic lesions strongly supports the diagnosis of CTEPH. In this situation, lung scintigraphy may be abandoned, and the patient should be referred for invasive diagnostics to confirm PH. However, normal CTPA does not exclude CTEPH and requires a further differential diagnosis of the cause of PH by pulmonary scintigraphy or arteriography. A proposed diagnostic algorithm for suspected CTEPH is shown in Figure 1.

Patients with suspected CTEPH based on clinical signs and echocardiographic features of right ventricular overload found after 3 months of optimal antithrombotic therapy should be referred to Reference Centers for the diagnosis and treatment of PH, or they should have ventilation-perfusion lung scintigraphy performed and be referred to reference centers if perfusion defects are found in areas of normal ventilation. A list of such centers is included at the end of the article.

PRINCIPLES OF TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The following methods are used to treat CTEPH [1]:

Procedural treatment

A. PEA is the treatment of choice for patients with surgical CTEPH. It involves separating the fibrous thrombus from the vessel wall and removing it. The plane of dissection usually runs at the level of the muscular layer of the artery. The procedure is performed in deep hypothermia, with temporary cardiac arrest. It should only be performed in experienced centers that specialize in this technique. In Poland, 30%–32% of patients with CTEPH are qualified for PEA [3, 16, 17] similar to Japan (23.5%) and in contrast to Western European countries (72.1%) and the US (87.2%) [18, 19]. The incidence of persistent CTEPH after PEA is about 50% in international registers, and 46% in Poland [2, 3]. In an international registry, among patients undergoing PEA, the mortality associated with PH was 3.5% at 32-month follow-up [18]. In contrast, the annual all-cause mortality rate in the US registry was 5.6% [19], while in a single-center study by Polish authors, peri-operative mortality was 9.1% [20].

B. BPA of the pulmonary arteries is a percutaneous procedure that involves unclogging and/or dilating the pulmonary arteries in areas occupied by organized thrombus using a balloon catheter. In an international registry, among patients undergoing BPA, the mortality associated with PH was 1.8% at 32-month follow-up [18]. In the Polish BNP-PL registry, the 3-year survival rate was 92.4%; perioperative complications, such as lung damage, were reported in 6.4% of sessions [21]. Multiple treatment sessions per patient are usually required to achieve clinical and hemodynamic improvement. The procedure should be performed in expert centers for PH.

Pharmacotherapy

A. Anticoagulant treatment is recommended indefinitely in all patients with CTEPH, including after PEA or BPA. Given the long experience, vitamin K antagonist (VKA) with a target international normalized ratio (INR) of 2.0–3.0 is standardly recommended. However, register studies indicate an increasingly common use of oral non-VKA anticoagulants in patients with CTEPH; in Poland, 50% use this group of anticoagulants, and 30.8% use VKA [2, 3]. Observational studies [22, 23] have found no differences in the efficacy and safety of these two groups of drugs. The exception is patients with antiphospholipid syndrome, in whom VKA is recommended [2].

B. Pulmonary artery-targeted treatment with riociguat, a soluble guanylyl cyclase stimulator, and the prostacyclin analog treprostinil in a subcutaneous form, have been registered for the treatment of inoperable CTEPH

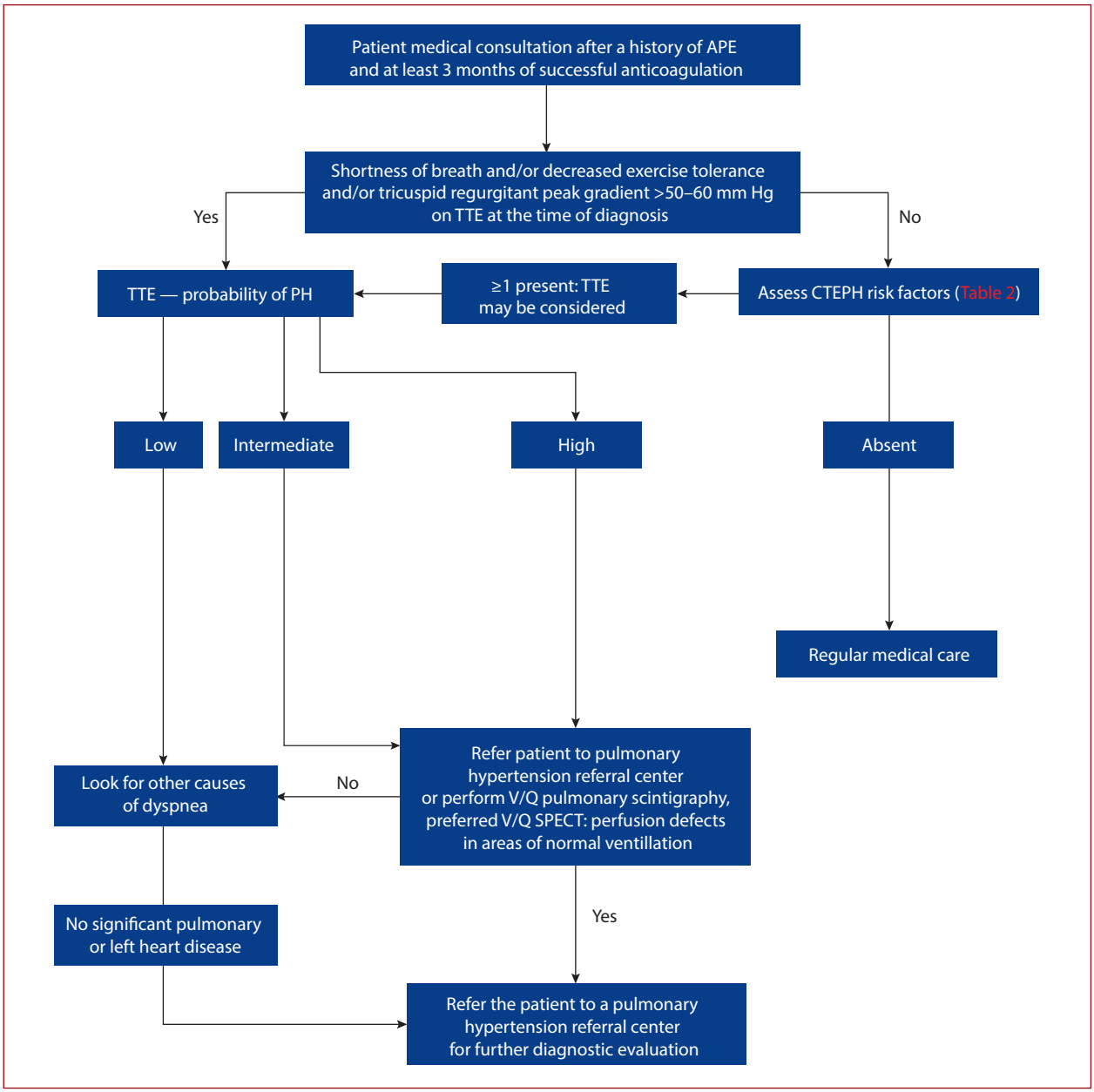

Figure 1. A proposed diagnostic algorithm for suspected CTEPH

Abbreviations: SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography; V/Q scintigraphy, ventilation-perfusion scintigraphy; other — see Table 1

or CTEPH persistent after PEA because of positive results from multicenter randomized trials [24, 25]. Riociguat is recommended for patients in World Health Organization (WHO) functional class II–III and treprostinil in functional class III–IV. Currently, only riociguat is reimbursed in Poland under the National Health Fund CTEPH Treatment Program, whereas treprostinil may be used only under the procedure of emergency access to drug therapies. Treatment should be provided at reference centers for PH.

C. Oxygen therapy for hypoxemia (PO_2 <60 mm Hg, arterial blood oxygen saturation <91%) [1].

D. Diuretics for fluid retention [1].

Treatment should be individualized for each patient by an interdisciplinary CTEPH team consisting of a surgeon experienced in PEA (in Poland the procedures are performed in cardiac surgery centers), an interventional cardiologist experienced in BPA procedures, and a cardiologist experienced in treating PH. The choice of treatment method is based on the evaluation of the location and extent of thromboembolic lesions (the surgical aspect of surgery), the stage of the disease, hemodynamic parameters, additional conditions, and the benefit-risk ratio (the medical aspect of surgery). In surgical patients, PEA is the method of choice, given its long usage and proven good long-term outcomes. In symptomatic non-operative patients, as well as in symptomatic patients with persistent or recurrent PH after PEA, treatment with riociguat is indicated, i.e., patients in WHO functional class II–III. Combination therapy with

treprostinil should also be considered in patients with WHO class III–IV CTEPH. BPA should be considered in symptomatic patients with inoperable, persistent, or recurrent PH after PEA. This procedure should only be performed at experienced centers.

COVID-19 RELATED TO CTEPH

SARS-CoV-2, the causative agent for COVID-19, led to a global health crisis in 2020 [26]. In addition to pneumonia, clinical characteristics of COVID-19 include multidirectional and often serious consequences, also involving the cardiovascular system. The development of thrombi in the pulmonary circulation is important in this context. The potential mechanism is determined by the local coagulative effect and inflammatory changes triggered by viral infection, with the coexistence of endothelial cell dysfunction in the microvascular segment of the pulmonary circulation. However, the classical profile of venous thromboembolism is also determined by predisposing factors such as immobilization, venous catheters, hypoxemia, and chronic heart failure. From a general perspective, an assessment of the frequency of thromboembolic lesions associated with SARS-CoV-2 co-infection remains considerably difficult; observations were mostly retrospective, study groups were selected based on heterogeneous criteria, and varied diagnostic strategies were used. A systematic review and meta-analysis of 23 studies with a population size of 7178 found a prevalence of 1.6%–65.0% for patients with APE who were hospitalized in general wards (pooled incidence value) 14.7%, and 4.2%–75% in intensive care units (pooled incidence value, 23.4%) [27]. Lesions were more frequently found at the level of segmental and subsegmental arteries. In contrast, a Cochrane review of 16 studies including 7700 hospitalized patients found a weighted mean incidence of 7.4% for venous thromboembolism and 4.3% for APE [28]. An opposed methodology was used in a study from Spain, where the analysis was conducted among 74 814 patients with COVID-19, who presented in 62 hospital emergency departments, which accounts for about 20% of all units in the country. APE was found in 4.92% of patients, and the standardized rate was 9-fold higher than the corresponding diagnosis in the population without coexisting COVID-19 lesions [29].

It is even more complicated to determine the effect of SARS-CoV-2 mass infections on CTEPH. The authors of a brief report from the United Kingdom observed a 32% reduction in the number of patients presenting to a central coordinating center for CTEPH confirmation, compared to the 3 years prior to the onset of the COVID-19 pandemic in 2020 [30]. There are several potential causes for this:

- different hypothesized pathogenic mechanisms;
- a lower risk of CTEPH associated with the more distal location of thrombi and their structural distinctiveness in the event of infectious complications;
- hypothesized higher efficacy of anticoagulant treatment;
- the need for a longer follow-up;
- reduced prevalence of classical predisposing factors for thromboembolism, i.e., elective surgery or air travel; and
- severe overburdening of the health care system worsening the diagnostic process of CTEPH [28].

COVID-19-conditioned mortality rates should also be considered. A brief survey of patients with PH from 47 centers across 28 countries worldwide has been published [31]. Unfortunately, the data correspond to the early stage of demographic observations (April 17, 2020 to May 10, 2020) and suffer from an obvious lack of complete representativeness. SARS-CoV-2 infections affected 70 patients at 19 centers. The overall mortality rate was 19%. It was 14% in patients with CTEPH and 20% in patients with PAH. Thus, the analysis showed a significantly worse prognosis and higher risk in the PH patient population compared to the general SARS-CoV-2 infected population. Patients with CTEPH in the era of the COVID-19 pandemic experience significantly increased levels of anxiety and depression, which may result in reduced frequency of personal visits to treatment centers [32].

Analyzing the literature data and pathophysiological changes caused by SARS-CoV-2 infection, one cannot exclude the possibility of a higher incidence of CTEPH in the future. In addition, the delay in diagnosis caused by the pandemic may result in significant disease progression at the time of CTEPH diagnosis and thus a poorer prognosis for patients.

CONCLUSION

CTEPH is a rare but very dangerous sequela of APE that can occasionally occur in patients without a history of an APE. The incidence of CTEPH after a history of APE is approximately 1%–4%. In Poland, hundreds of patients develop the disease each year; if epidemiological data for developed countries (e.g., the US, the United Kingdom) are applied to the Polish population, the incidence should be assumed at the level of about 250 patients/year. The COVID-19 pandemic can be expected to result in a higher incidence of CTEPH, and delayed diagnosis is anticipated to result in the development of the more advanced stages of the disease. The prognosis for people with CTEPH depends on proper diagnosis. The lack of a diagnosis and appropriate treatment significantly reduces the quality of life and inevitably leads to death in patients with CTEPH. It is important to identify patients who present with symptoms suggestive of CTEPH after an incident of APE. Therefore, every patient should visit their doctor after 3 months of anticoagulation treatment following diagnostic confirmation of an APE. Initial suspicion of CTEPH should be made by physicians caring for patients in out-patient clinics. When features of right ventricular overload are identified on TTE performed after at least 3 months of optimal anticoagulation therapy, these patients should be referred to reference centers for the diagnosis and

treatment of CTEPH. There are now effective surgical and pharmacological treatments for CTEPH, improving the quality of life and prognosis of patients. All forms of CTEPH therapy are available in Poland.

THE MANAGEMENT OF APE: INFORMATION FOR THE PRIMARY CARE PHYSICIAN

We emphasize the following points concerning the clinical management of APE, with a focus on points of care for the physician.

- First, the patient requires periodic medical follow-up after an incident of APE.
- Each patient should have a follow-up medical visit 3–6 months after an incident of APE. During the visit, determine whether anticoagulation treatment should be continued and suggest a follow-up schedule. TTE should be performed in patients with dyspnea.

Clinicians should suspect CTEPH and refer the patient for further diagnosis under the following circumstances: (1) exertional dyspnea or signs of right heart failure in a patient with a history of APE; or (2) persistent exertional dyspnea in a patient after at least 3 months of antithrombotic therapy, especially when there are signs suggestive of PH on a follow-up TTE.

Patients should be referred for assessment 3 months after an incident of APE in the cardiology or internal medicine outpatient clinic preferably in the center where the patient was treated. A patient with suspected CTEPH should be referred to a CTEPH referral center (see the list of centers attached to this document).

LIST OF POLISH CENTERS THAT DIAGNOSE PATIENTS WITH SUSPECTED CTEPH

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LIST OF LABORATORIES PERFORMING LUNG SCINTIGRAPHY

The list of laboratories performing pulmonary scintigraphy can be found in Supplementary files and on the website of the Pulmonary Circulation Section of the Polish Cardiac Society at: http://www.ptkardio.pl/Lista_pracowni_wykonujacych_scyntygrafie_pluc-2718.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: MC received grants or personal fees from Bayer, Boehringer-Ingelheim, MSD, and Pfizer. MK received speaker fees and travel grants from MSD, AOP Orphan, Janssen, Pfizer, and Pfizer. GK received grants or personal fees from Janssen-Cilag, MSD, Bayer, and AOP Orphan. ŁC participated on Advisory Board and received lecture honoraria from MSD, and lecture honoraria from AOP Orphan, Janssen, and Actelion and Ferrer. KK received lecture honoraria, travel expenses coverage, and consultancy fee from MSD, Boehringer Ingelheim, and Bayer. PP participated on Advisory Board and received lecture honoraria from MSD, AOP, Boehringer Ingelheim, Bayer, and Pfizer. AT received lecture honoraria from AOP, Bayer, MSD, Janssen, and Pfizer; and consultancy fees from Bayer, MSD, and Janssen. PB, KMS, TMK, AB, DZ, and EM declare no conflict of interest.

Funding: None.

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