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The role of pharmacotherapy in the treatment of chronic thromboembolic pulmonary hypertension (RCD code: II-1A.5)

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating disease caused by chronic obstruction of major pulmonary arteries. The median age of patients at diagnosis of CTEPH is 63 years and both genders are equally affected. The symptoms are usually nonspecific, particularly in the early stages of the disease, which significantly delays the diagnosis. All patients with pulmonary hypertension (PH) of the unknown aetiology should be diagnosed for CTEPH, even without the information on pulmonary embolism in the medical history. Ventilation-perfusion scintigraphy of the lungs has the highest sensitivity in the diagnosis of CTEPH. A positive result of scintigraphy suggestive of CTEPH is not enough to diagnose the disease. Right heart catheterization and angiography of the pulmonary arteries definitively confirm the diagnosis. All patients with CTEPH should receive chronic oral anticoagulation using generally vitamin K antagonists (warfarin, acenocumarol). Pulmonary endarterectomy (PEA) is the only effective treatment for eliminating the cause of the disease. However, not all patients can be referred for pulmonary endarterectomy surgery. According to data from the European CTEPH Registry of the years 2007-2009, over 40% of patients is not subjected to the operation mainly due to the distal location of thromboembolic changes. Currently, riociguat is the only approved therapeutic agent for the pharmacological treatment of inoperable/persistent CTEPH. In some cases, Off-lebel use of drugs approved for PAH may be considered in symptomatic patients with inoperable CTEPH/persistent PH after PEA. Recent advances in balloon pulmonary angioplasty make it a promising therapeutic alternative for selected patients with non-operable CTEPH. JRCD 2015; 2 (2): 38–42

Key words: riociguat, pulmonary endarterectomy, pulmonary embolism

Introduction

Pulmonary hypertension is a rare cardiovascular disease (complex group of diseases), of the unexplained aetiology and the complex pathomechanism. It is defined as the increased mean pressure in the pulmonary artery ≥ 25 mmHg at rest, determined through right heart catheterization [1]. Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the types of PH (group 4 by classification of Nice from 2013) [2]. It can be diagnosed in a patient with the properly documented chronic organized thromboembolic material in the pulmonary arteries of the elastic type – the main, lobar, segmental, subsegmental [3].

This type of pulmonary hypertension is a rare, but serious complication of pulmonary embolism, which if untreated leads to the progressive right heart failure and death. It is estimated that only 0.1–0.5% of patients after an episode of acute pulmonary embolism develop CTEPH [3]. In the vast majority of patients with pulmonary embolism, thrombi dissolve under the influence of the endogenous fibrinolytic system, and hemodynamic parameters normalize over time. The factors that increase the risk of CTEPH include idiopathic PE, the recurrent nature, the large perfusion losses in imaging studies, and younger age of patients [1,3].

Pathogenesis

The pathogenesis of CTEPH is not fully explained. It is believed that the primary mechanism of its formation is abnormal resorp-

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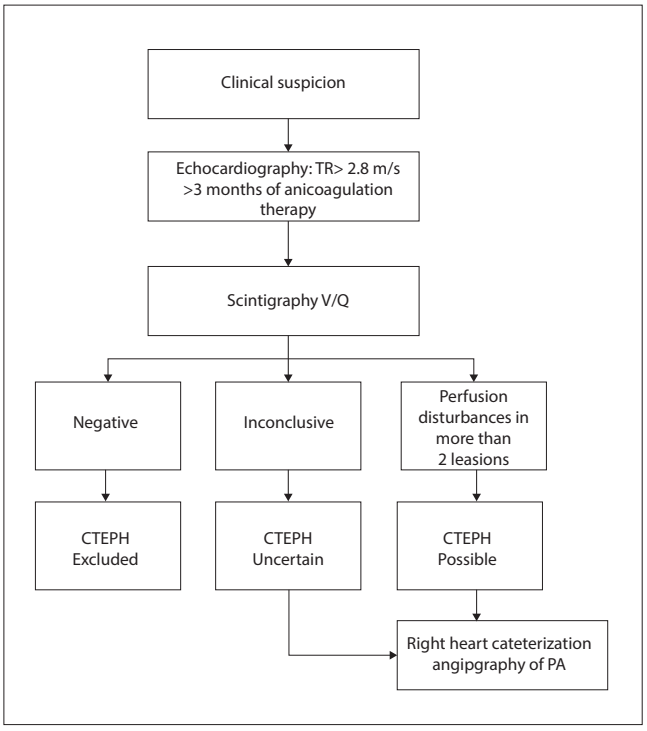

Figure 1. Diagnostic algorithm of Chronic thromboembolic pulmonary hypertension (CTEPH). TR – tricuspid regurgitant velocity, V/Q – ventilation-perfusion, PA – pulmonary artety [20]

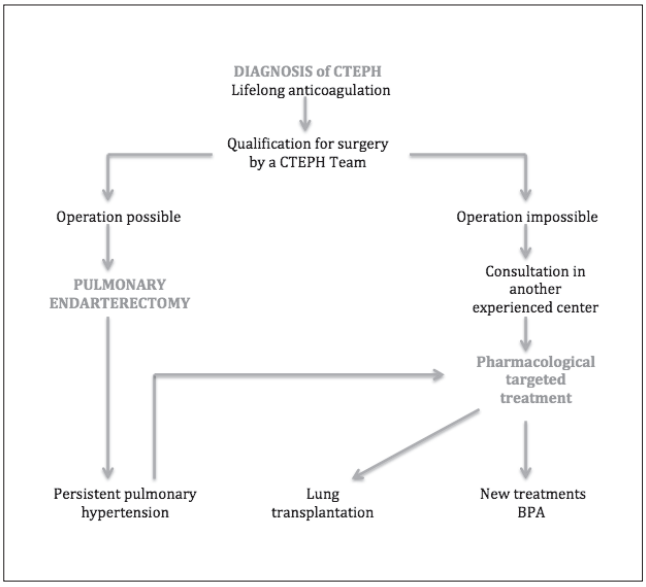

Figure 2. Treatment algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). BPA – pulmonary balloon angioplasty, CTEPH Team – a multidisciplinary team of specialists with experience in treating patients with CTEPH

tion of the thrombi remaining after an acute episode of thromboembolism, which then undergo fibrosis, glaze, and form a band of the connective tissue. However, authors of several articles indicate that only about 50% of patients have episodes of acute pulmonary embolism [3,6], therefore they hypothesize that in situ thrombosis could be another pathomechanism [7]. CTEPH may also be a consequence of repeated poorly symptomatic episodes of PE [1,3,10]. Regardless of the pathomechanism, the clinical symptoms appear only when > 40% of the pulmonary vascular bed is closed [3]. The high pressure in the pulmonary bed damages the endothelium and causes its dysfunction, which if followed by remodelling of the small resistance arterioles in the pulmonary circulation. This contributes to the disease progression. Histopathological changes in the distal pulmonary vessels include proliferation of the intima and myocytes, the thickening of the media and the formation of plexiform changes [1].

In one of their studies Berger et al. mentioned that histopathological changes in the small pulmonary arteries, revealed in biopsy specimens collected from patients with chronic thromboembolic pulmonary hypertension, were almost identical to the changes observed in patients with idiopathic pulmonary hypertension. These results suggest that PAH and CTEPH may share the common pathophysiological pathways. Like in PAH, patients with CTEPH demonstrate an increase in the concentration of endothelin, the increased expression of receptors for endothelin type B located on the vascular smooth muscle cells, reduced concentration of nitrogen oxide and prostacyclin [3,10]. Hence, one may expect that the specific agents used in the PAH may have a beneficial effect in patients with CTEPH, as well.

Symptoms and diagnosis

One of the main symptoms of CTEPH is increasing exertional dyspnoea, a decrease in exercise tolerance, occasional fainting, and finally at an advanced stage the symptoms of the right heart failure. The symptoms are usually nonspecific, particularly in the early stages of the disease, which significantly delays the diagnosis [1,2,3,7].

All patients with pulmonary hypertension of the unknown etiology should be diagnosed for CTEPH, even without the information on pulmonary embolism in the medical history. Ventilation-perfusion scintigraphy of the lungs has the highest sensitivity in the diagnosis of CTEPH. In patients with the normal lung chest X-ray perfusion scintigraphy is recommended. A negative result excludes the diagnosis of CTEPH with almost 100% certainty [7,8]. However, a positive result of scintigraphy suggestive of CTEPH is not enough to diagnose the disease. Right heart catheterization and angiography of the pulmonary arteries definitively confirm the diagnosis [1,2,7].

Treatment

All patients with CTEPH should receive chronic oral anticoagulation using generally vitamin K antagonists (warfarin, acenocumarol). INR should be 2–3. This treatment aims to prevent recurrent thrombosis in situ in the pulmonary arteries and venous thromboembolism. Home oxygen therapy and diuretics are the supportive therapy, but there are no specific studies on their impact on the survival of patients.

Pulmonary endarterectomy (PEA) is the only effective treatment for eliminating the cause of the disease. It involves the removal of

Table 1. The table below summarizes the results of major clinical trials conducted in patients with CTEPH using specific medications for PAH

The first author of the study, year of publication	Sample size [n]	Active ingredient	Type of study	Results
Olschewski, 2002	57	Illoprost	RCT	A 3-month follow-up showed an improvement of the distance in the 6MWD test in the group receiving Illoprost. 4% in the group taking Illoprost and 13.7% in the placebo group did not complete the study because of deterioration (4 patients died). A 12-month follow-up revealed an improvement in the functional class, decreased dyspnoea and improved quality of life [16].
Carbol, 2007	27	Epoprostenol	-	After 3 months, there was an improvement in WHO-FC by one class (11 patients), an increase of the distance in 6MWD test by 66m, an improvement in hemodynamic parameters (PVR, mPAP, TPR, PVR, CI). Survival after 1, 2, 3 years of observation was 73%, 51%, 41%, respectively [11].
Suntharalingam, 2008	19	Sildenafil	RCT	After 3 months of follow-up, there were no significant differences in both groups (placebo/sildenafil) in the exercise capacity. The group receiving sildenafil noted a significant improvement in the WHO-FC and PVR. After 12 months of follow-up (n=17 taking sildenafil) a significant improvement was reported in 6MWD, PVR, CI, Np-pro BNP, as well as the quality of life (QOL) [12].
Jais X, 2008	157	Bosentan	RCT	A 4-month follow-up revealed an improvement in haemodynamic parameters in the group receiving bosentan, but no improvement in the exercise capacity [13].
Ghofrani, 2010	41	Riociguat	-	A 3 month follow-up reported significantly improved hemodynamic parameters (PVR, CI, mPAP), and exercise capacity (an increase in 6MWD distance, reducing the symptoms of breathlessness by 1 point according to in the Borg scale) [14].
Ghofrani, 2013	261	Riociguat	RCT	After 4 months, the group receiving riociguat reported a significant improvement in exercise capacity (6MWD), hemodynamic parameters (PVR, mPAP, CO), as well as a decrease in NT-pro-BNP and the WHO-FC compared to the placebo group [15].
Sokoro-Sajer, 2007	25	Tresprostnil	-	After 6 months of follow-up, the group receiving treprostinil showed an improvement in exercise capacity (6MWD) and WHO-FC, a drop of PVRm, an improvement in CO, and a decrease in NT-pro BNP [17].
Hoeper, 2005	19	Bosentan	-	After 3 months of follow-up, there was an improvement in hemodynamic parameters (PVR), no improvement in WHO-FC and VO2 peak, an increase in the 6MWD distance and a decrease in the level of NT-pro-BNP [18].

6MWD – 6-minute walk test, WHO-FC – the functional class according to WHO, PVR – pulmonary vascular resistance, mPAP – mean pressure in the pulmonary artery, TPR – total pulmonary resistance, CI – cardiac index, AQoL – Australian Assessment of Quality of Life, , CO – cardiac output, VO2 peak – maximal oxygen uptake

emboli from the pulmonary arteries and restoring the blood flow. The effective PEA is associated with the reduced mortality and leads to a permanent improvement in the pulmonary hemodynamics and exercise capacity of patients. The analysis of the international CTEPH register showed that mortality after PEA was 5% within a year after treatment [7]. The main criterion in deciding whether to perform surgery is the location of thromboembolic changes. However, there are no specific eligibility criteria. It is assumed that the available surgical techniques allow for the removal of the changes from the main and lobar arteries, but more experienced cardiac surgeons perform endarterectomy within the segmental arteries. The clinical indications for PEA include increasing exertional dyspnoea and limited exercise tolerance in the class at least II by World Health Organization or New York Heart Association (WHO/NYHA). The condition for considering the PEA includes the lack of severe comorbidities, but in patients with risk factors for ischemic heart disease coronary angiography should be performed prior to pulmonary endarterectomy [1,5]. However, not all patients can be referred for pulmonary endarterectomy surgery. According to data from the European CTEPH Registry of the years 2007–2009, over 40% of patients is not subjected to the operation mainly due to the distal location of thromboembolic changes.

In recent years, clinical studies have shown that the use of specific drugs for the treatment of pulmonary arterial hypertension can have beneficial effects in patients with CTEPH, in which, due to the location of changes it is not possible to perform pulmonary endarterectomy surgery, it is contraindicated due to significant comorbid conditions, there is a high operational risk due to poor hemodynamic parameters before pulmonary endarterectomy, or if pulmonary hypertension persists after PEA (persistent pulmonary hypertension).

Of all the studies on the efficacy of the pharmacological treatment in patients with inoperable CTEPH/persistent PH after PEA two are of the utmost importance.

The first randomized controlled trial (RCT) in CTEPH was the BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension) study with bosentan. The study compared bosentan, which is an orally active dual endo-

Table 2. The primary and secondary end-point of the CHEST-1 study

End Point	No of patients	Placebo	No of patients	Riociguat
Primary				
6MWD	88	-6 m	173	+46m
Secondary				
PVR	82	23	151	-246
Nt-pro-BNP	73	+76	150	-444
WHO-FC	87	13 patients (15%) moved to lower class, 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	57 patients (33%) moved to lower class, 107 (62%) stayed in same class, 9 (5%) moved to higher class
Borg scale [A]	88	0.2	173	–0.8
EQ-5D scale [B]	87	–0.08	172	0.13
LPH scale [C]	86	–2	170	–6

[A].The Borg dyspnea scale ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea. [B]. Scores on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire) range from 0 to 105, with higher scores indicating worse quality of life. [C]. Scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) range from –0.6 to 1.0, with higher scores indicating a better quality of life. 6MWD-6 min walk distance test, PVR-pulmonary vascular resistance, WHO-FC-The World Health Organization functional class. Nt-pro-BNP- N-terminal of the prohormone brain natriuretic peptide

thelin receptor antagonist, with placebo conducted in 157 patients with inoperable or persistent/recurrent CTEPH over the period of 16 weeks. The co-primary end-points included the change from baseline in pulmonary vascular resistance (PVR) and the change from baseline in 6MWD after 16 weeks of therapy. The secondary end-points included WHO functional class (WHO-FC) and time to the clinical worsening. N-terminal pro-brain natriuretic peptide (NT-proBNP) was evaluated as an exploratory end-point. The study showed a significant decrease in PVR ($p<0.0001$) and an increase in the cardiac index ($p=0.0007$) for bosentan-treated patients versus placebo. There was also a significant decrease in the NT-proBNP levels ($p=0.0034$). However, bosentan therapy did not significantly improve 6-minutes walking distance (6MWD), WHO-FC or time to the clinical worsening. Bosentan had similar effects on 6MWD and PVR in inoperable patients versus those with persistent/recurrent CTEPH. Given the lack of demonstrable clinical benefits, bosentan is not currently approved for the use in patients with CTEPH.

The largest RCT in the medical therapy of CTEPH to date is the CHEST-1 (Chronic Thomboembolic Pulmonary Hypertension Soluble Guanylate Cyclase- Stimulator Trial-1) study with riociguat, which became the first to achieve clinically meaningful primary endpoints. 261 patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA were randomised to receive placebo or riociguat, three times daily. The primary endpoints included the mean change in 6MWD after 16 weeks. The results showed that 6MWD increased by 47m in the riociguat group, versus a decrease of 6m in the placebo group. The secondary end-point of the changes in PVR was also met. There was a significant increase in PVR in the riociguat group, versus the placebo group. The study also revealed a significant improvement in the NT-proBNP levels and WHO-FC. There was no difference in the incidence of clinical worsening events between the riociguat group and the placebo group. The CHEST-2 study was a continuation of CHEST-1, and it was offered to 234 patients, who completed the CHEST-1. Finally, 237 patients were enrolled. After one year an improvement in 6MWD observed in the CHEST-1 study maintained and the survival was 97%. The safety profile was good, in the long term observation. Only 5% of patients withdrew from the study due to adverse

Table 3. Recommendations for patients with Chronic thromboembolic pulmonary hypertension [20]

Recommendations	Class/Level
All patients with persistent dyspnea after an episode of PE should be diagnosed towards CTEPH.	IIa/C
Screening for CTEPH in asymptomatic patients after an episode of PE is not currently recommended	III/C
The therapeutic decision should be made by a multidisciplinary team of specialists who have experience in treating these patients-CTEPH Team.	I/C
All patients with CTEPH should receive lifelong oral anticoagulation.	I/C
In patients with CTEPH surgical treatment is recommended, if possible.	I/C
Riociguat is recommended for patients with inoperable/persistent PH after PEA. A decision should be made by CTEPH team, including at least one experienced surgeon in the PEA.	I/B
Off-lebel use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH Team.	IIb/B

Class –class of recommendation, level-level of evidence

events (AEs), which included syncope, haemoptysis or pulmonary haemorrhage.

Currently, riociguat is the only approved therapeutic agent for the pharmacological treatment of inoperable/persistent CTEPH.

Recent advances in balloon pulmonary angioplasty make it a promising therapeutic alternative for selected patients with non-operable CTEPH [20, 21].

Summary

Table 3 below summarizes the recommendations for treatment in CTEPH.

CTEPH is a rare complication of acute pulmonary embolism, it can also occur in patients who do not have a history of acute pulmonary embolism. Ventilation scintigraphy/lung perfusion should be the basic and the first diagnostic tool. A negative result virtually excludes the diagnosis with almost 100% certainty. At the same time, the presence of perfusion defects in scintigraphy does not confirm CTEPH. Further diagnostics is necessary, which should involve a number of studies, including right heart catheterization and angiography of the pulmonary arteries. Each patient diagnosed with CTEPH ought to be considered for pulmonary endarterectomy, as it is the only effective treatment method for eliminating the cause of the disease, leading to cure. Pharmacological therapy should be considered in patients with inoperable/persistent CTEPH after PEA. Currently, riociguat is the only registered drug. Other PAH-specific drugs have not shown effectiveness in CTEPH, and they are still a subject to intensive clinical trials.

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