https://doi.org/10.38109/2225-1685-2017-4-86-99

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CARDIOPULMONARY EXERCISE TESTING IN RISK STRATIFICATION IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION AND CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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SUMMARY

In recent years the information about relevance of cardiopulmonary exercise testing (CPET) in complex assessment of pulmonary arterial hypertension (PAH) patients and chronic thromboembolic pulmonary hypertension (CTEPH) patients have been accumulating. Parameters of CPET, such as peak oxygen consumption (Vo2 peak) and ventilation equivalents (VE/Vco2) are very important in risk stratification in patients with PAH, also as distance in 6-minute walking test, the echocardiography and right heart catheterization results, N-terminal prohormone of natriuretic peptide according to the European Society of Cardiology and European Respiratory Society guidelines on diagnosis and treatment of pulmonary hypertension.

However, there are no parameters, which can be used in clinical practice to reflect the risk of mortality during 1 year in patients with CTEPH.

The aim of our study was to assess the role of CPET in risk stratification, achieving therapy goals and making decision about therapy escalation in patients with PAH and CTEPH.

Results of our pilot study demonstrated, that CPET parameters are the reliable markers to reflect the PAH and CTEPH progression. The CPET is necessary for pathogenic therapy efficacy assessment and for making decision of therapy escalation in patients with PAH, also as in CTEPH patients. The critical role of CPET in risk stratification in PAH and CTEPH patients should be emphasized.

Keywords: *cardiopulmonary exercise test, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, risk stratification*

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For citation: Taran I.N., Valieva Z.S., Martynyuk T.V., Chazova I.Ye. Cardiopulmonary exercise testing in risk stratification in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Eurasian heart journal. 2017, November 25; 4:94-99 [in Russian].

INTRODUCTION

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are diseases most often diagnosed at a late stage with functional class (FC) of pulmonary hypertension (PH) III or IV according to the World Health Organization (WHO) classification, leading to severe right ventricular (RV) failure and death.

Pathophysiological signs of PAH and CTEPH include obliteration and obstructive reconstruction of small pulmonary arteries and arterioles, vascular inflammation and remodeling, endothelial dysfunction, that result in progressive elevation of pulmonary vascular resistance (PVR) and increase of pulmonary artery pressure (PAP) [1; 2].

Due to non - specificity of clinical picture of PH patients, such method as cardiopulmonary exercise testing (CPET) can be useful in differential diagnosis of PH etiology, severity assessing and revealing the pathophysiological mechanisms, underlying exercise intolerance [3, 4]. CPET parameters provide useful prognostic information for patients with PAH and CTEPH [3, 5].

Treatment of patients with PAH is aimed at achieving the following therapeutic goals: being WHO FC I/II; normalization of right heart size and RV function, defined as a right atrial area (RAA) <18 cm2 and the absence of pericardial effusion (according to transthoracic echocardiography (EchoCG) and magnetic resonance imaging (MRI)); mean right atrial pressure (mRAP) < 8 mmHg; cardiac index (CI) ≥ 2.5 L/min/m2 and mixed venous blood saturation (Svo2) > 65 % according to the right heart catheterization (RHC); 6-minute walking distance (6MWD) >440 m; peak oxygen consumption (VO2 peak) >15 mL/kg/min; ventilatory equivalents for carbon dioxide (VE/Vco2 slope) <36; and normalization of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels [6, 7] (Table 1). The risk of 1-year mortality of patients with PAH is determined by a complex assessment of above - mentioned parameters.However, currently there are no parameters that determine the risk of 1 –year mortality and can be used in clinical practice in CTEPH patients.

It is interesting to assess the role of CPET in 1- year mortality risk stratification, evaluation of the efficacy of the pathogenic therapy and making decision about therapy escalation in patients with PAH and CTEPH, which was the purpose of our study.

MATERIALS AND METHODS

This pilot study meets all ethical standards. Before the enrollment, all patients signed informed consent.

Diagnosis of PAH and CTEPH was established on the basis of complex clinical and instrumental examination, including history, physical examination, full laboratory blood test data (including blood analysis for antiphospholipid and antinuclear antibodies), electrocardiography in 12 leads, transthoracic EchoCG, ultrasound of abdominal cavity organs, chest X-ray examination, examination of respiratory function (spirometry), ventilation/perfusion scan, MRI in phase-contrast mode, computed tomography (CT) with pulmonary angiography and heart CT with intravenous contrast, RHC with acute vasodilator testing with nitric oxide inhalation 20-40 ppm (for patients with idiopathic pulmonary arterial hypertension (IPAH) and PAH induced by drugs and toxins) and selective pulmonary angiography (for patients with CTEPH). The status of the operability in CTEPH patients was evaluated by multidisciplinary team of experts, including cardiologists, radiologists and surgeons. For functional status assessment the 6MWD test was performed with determination of the dyspnea level according to the Borg scale and the desaturation index.

CPET was conducted on cycle ergometry SCHILLER CARDIOVIT CS-200 Ergo-Spiro with Ganshorn Power Cube gas analyzer using a breath-by-breath breathing system to record gas exchange data for more than 10 intervals.

CPET with submaximal exercise was performed at the end of the 1st week of hospitalization in case of stabilization of the main parameters of ventilation and hemodynamics, taking into account clinical and electrocardiographic contraindications for stress test conduction using the CPET method in the breath-by-breath mode. In this mode, the amount of O_2 and CO_2 was taken into account during each respiratory cycle and was then automatically recalculated for 1 min. ventilation: Vo_2 is the oxygen consumption rate and Vco_2 is the carbon dioxide output rate. Exercise was stopped when patient felt dizziness, chest pain, or severe dyspnoea at submaximal heart rate (HR). Test protocol consisted of 3 minutes of rest, followed by 5-7 minutes of pedaling at 60 rpm with sequential increase of load from 5 to 25 Watts to the maximum tolerated, followed by 5 minute period of recovery. The mean duration of CPET was 9 minutes. Peak VO_2 was defined in the last 30 seconds of peak exercise.

Table 1. Risk stratification of 1- year mortality in patients with PAH

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5-10%	High risk >10 %
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Rare	Recurrent
WHO FC	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	VO_2peak>15 ml/min/kg (65% pred.) VE/VCO_2slope<36	VO_2peak11-15ml/min/kg (35-65%) VE/VCO_2slope36-44,9	VO_2peak<11ml/min/kg(<35% pred.) VE/VCO_2slope >45
BNP/ NT-proBNP plasma levels	BNP <50 ng/l Nt-proBNP<300 ng/l	BNP 50-300 ng/l Nt-proBNP300-1400 ng/l	BNP >300 ng/l Nt-proBNP>1400 ng/l
Imaging (echocardiography, CMR)	RA area <18 cm No pericardial effusion	RA area18-26 cm^2 Noor minimal pericardial efussion	RA area >26 cm^2 Pericardialeffusion
Haemodynamics	RAP <8 mmHg CI>2,5 l/ min/m^2 Svo_2>65%	RAP 8-14 mmHg CI>2,0-2,4 l/ min/m^2 Svo260-65%	RAP >14 mmHg CI>2,0 l/ min/m^2 Svo_2<60%

Oxygen pulse (O_2 pulse) peak was calculated through the ratio of Vo_2 peak to HR. The anaerobic threshold (AT) was determined by the slope method (linear regression method by changing the slope of the Vco_2 / Vo_2 curve). VE / Vco_2 was determined by a linear regression analysis of the ratio of minute ventilation and carbon dioxide emission.

Statistical analysis of the data obtained was carried out using the Statistica v. 10.0 for Windows software package (StatSoftInc., USA), and allowed for both parametric and non-parametric analysis. The Spearman correlation coefficient was used to determine the correlation between the parameters. The results of the studies are presented as mean value and standard deviation (SD).

RESULTS OF THE STUDY

74 patients were included in the study: PAH (n = 57) and CTEPH (n = 17). The PAH group consisted of 44 patients with IPAH, 10 patients with PAH associated with congenital heart disease, 2 patients with PAH associated with connective tissue diseases, and 1 patient with PAH induced by drugs and toxins. In CTEPH group 14 patients were inoperable, 2 operable patients, 1 patient had residual pulmonary hypertension. Patients included in the study were hospitalized in the Department of Pulmonary Hypertension and Heart Diseases of the Scientific Medical Research Center of cardiology of the Ministry of Health of Russian Federation, Scientific Research Institute of Clinical Cardiology of A.L. Myasnikov.

Characteristics of patients are presented in Table 2.

At the time of CPET performing in the PAH group 19% of patients did not receive pathogenetic therapy previously, 32% received monotherapy, 35% received double combination pathogenetic therapy, and 14% received triple combination pathogenetic therapy. 34% of patients with CTEPH at the time of CPET performing did not receive pathogenetic therapy, 66% were on monotherapy.

The annual risk of mortality for patients with PAH is estimated by evaluation of the clinical examination data, functional tests, biochemical markers, EchoCG parameters and RHC: low risk (<5%), intermediate risk (5-10%), high risk (> 10%), respectively (Table 1).

Table 2. Demographic, functional and hemodynamic characteristics of patients

Parameters		
	PAH patients (n=57)	**CTEPH patients (n=17)**
Age , years	43,9+10,5	53,7+8,6
Sex (n female)	n=50	n =11
Functional status		
6MWD,m	414+112	402+81
FC (WHO) I/II(n)	9/20	0/10
FC(WHO) III/IV (n)	27/1	7/0
Cardiopulmonary exercise testing		
Time of exercise, min	9 +4	9,7+3,8
Work rate, W	50+21,7	53+25
O_2 pulse peak, %	6+2,2	7,38+1,8
VO_2 peak, ml/kg/min Vo_2 peak %	11,1+4 45+15	10,3+2,3 48+15
VE/VCO2 slope	45,3+16	42,7+9
VD/VT peak	0,19+0,07	0,17+0,06
PET Co_2 peak, mmHg	26,1+7,7	26,4 +7,8
Vo_2/ WR, ml/ min/W	13,2+11,9	19,7+13,9
Echocardiography		
RA area, cm^2	21,6+7	22,4+6,2
RV size ,cm	3,6+0,7	3,2+0,4
IVC, cm	2,0+0,3	2,06+0,44
Right heart catheterization		
mPAP , mmHg	55+14,6	47,2+12,7
mRAP, mmHg	6,4+4,7	4,9+2,4
SVo2 ,%	61,9+9	60+9
CI, l/min/m^2	2+0,5	2,1+0,6
PVR, dyn*s*cm^{-5}	1208+596	764+400

** Constant variables are presented as the mean ± SD.PAH – pulmonary arterial hypertension; CTEPH – chronic thromboembolic hypertension; FC (WHO) – functional class by World Health Organization classification, 6MWD- 6-minute walking distance, Vo_2 – oxygen consumption; Vo_2 peak- oxygen consumption at peak exercise; AT = anaerobic threshold; O_2 pulse = peak VO_2/heart rate at peak exercise; VE – minute pulmonary ventilation; Vco_2- carbon dioxide output; VE/Vco_2 – ventilation equivalents slope; WR= work rate; VD/VT - dead space ventilation, RA - right atrium, RV –right ventricular; IVC –inferior vena cava; mPAP – mean pulmonary artery pressure; mRAP- mean right atrial pressure; SvO_2 - mixed venous blood saturation; PVR –pulmonary vascular resistance*

The CPET values of Vo2 peak > 15 ml / min / kg, VE / Vco2 slope <36, indicated a low-risk of mortality, values of Vo2 peak = 11-15 ml / min / kg, VE / Vco2 slope = 36-44,9 indicated an intermediate risk, and values of Vo2peak <11 ml / min / kg, VE / Vco2slope > 45 indicated a high-risk, respectively (Table 1).

According to the complex clinical and hemodynamic analysis of patients, we revealed, that the majority of patients with PAH had high risk of fatal events within 1 year 46% (n = 26), intermediate risk had 39% (n = 22), while 15% had low risk (Figure 1). Most of CTEPH patients had intermediate risk 54% (n = 9), 40% (n = 7) had high risk and only 6% were at low risk (Figure 2).

However, after CPET performing, we got the results, showing, that 9 additional patients (16%) with PAH and 5 patients (30%) with CTEPH, who had been previously in intermediate risk, had a high risk of annual mortality.

After CPET, an additional 6% of patients with PAH and 6% of patients with CTEPH, who had been previously in low-risk, were referred to intermediate risk (Figure 1, 2).

In patients with PAH a positive correlation was found between VE / Vco2 and PVR (r = 0.61, p = 0.003). In patients with CTEPH a negative correlation was found between VE / Vco2 and 6MWD (r = -0.46, p = 0.02).

After the risk stratification with CPET results in 9% of PAH patients, who previously did not receive pathogenetic therapy, a double combination pathogenetic therapy were initiated; in 25% patients, previously treated with monotherapy, a second pathogenetic drug was added, and patients, previously received a double combination pathogenetic therapy (9%), were recommended to receive triple combination pathogenetic therapy. A patient with IPAH with IV FC (WHO) was failure to achieve the treatment goals with three pathogenetic drugs with maximum doses, because of that she was directed to lung transplantation.

24 % of inoperable CTEPH patients started therapy with one specific drug, in 24% of cases a second specific drug was added, 12% of patients underwent percutaneous balloon angioplasty of the pulmonary arteries, and in 12% pulmonary endarterectomy was planned.

DISCUSSION

There are specific pathophysiologic and hemodynamic mechanisms, which result in a characteristic pattern of abnormalities observed during exercise testing in patients with PAH and CTEPH. Elevated PVR consequently leads to dead space (VD/VT) ventilation increase due to the reduced perfusion of well-ventilated alveoli. Elevated VE/Vco_2 primarily results from high VD/VT, although early-onset lactic acidosis, excessive ventilation (alveolar hyperventilation) from increased chemosensitivity, and altered partial pressure of Co2 (PaCo2) "set-point" also contribute to the disproportionate increase in minute pulmonary ventilation (VE) [8-12].

In healthy subjects, VD/ VT decreases during exercise as a result of increasing in tidal volume (VT), a response that is diminished or absent in patients with pulmonary vascular diseases as a result of severe ventilation–perfusion mismatching (high V/Q ratio) or a rapid shallow breathing pattern [9-11, 13].

It is known that in CTEPH patients with distal lesions, VD / VT correlates with exercise tolerance and is associated with survival [14].

In healthy people, the cardiac output (CO) increases during an exercise due to an increase in the oxygen demand of peripheral muscles and an increase in pulmonary blood flow, which is accompanied by vascular dilatation and a decrease in PVR [15]. The high vascular resistance requires an increased cardiac output during exercise, which leads to further increases in mean pulmonary artery pressure [16]. This progressive elevation in afterload limits the ability of the right ventricle to augment stroke volume [17], and therefore increases in cardiac output during exercise are strongly dependent on HR [18].

High right ventricular pressure and right ventricular dilation cause interventricular septal shifting, which, along with reduced pulmonary venous return to the left atrium, impairs left ventricular diastolic filling, systemic CO, and tissue oxygen delivery, contributing to the early onset of lactic acidosis and reduced AT [22] (Table 3, Figure 3).

Pathophysiology and mechanisms of exercise intolerance in pulmonary hypertension.

Pulmonary vascular obstruction, remodeling, and endothelial dysfunction result in high ventilation–perfusion mismatching (V/Q) and impaired cardiac output. Inefficient ventilation proposes high ventilatory demand, high VE/V CO2 and VD/VT, and low end-tidal pressure of carbon dioxide (PETCO2). Cardiac limitation and peripheral muscle abnormalities result in a low anaerobic threshold, early-onset lactic acidosis (lactate), and increased Vco2, which provide further stimulation for excessive ventilation. Ventilatory mechanical constraints on VT expansion also contribute to dyspnea during exercise.

Reduced Vo_2peak, AT, Vo_2 to work rate (WR) ratio, peak HR, and O_2 pulse (Vo_2/ HR) reflect impaired circulatory responses and are correlated to New York Heart Association FC and hemodynamic severity [8-10].

In patients with PAH and CTEPH the decrease of O_2 pulse is a reflection of stroke volume impairment and the dependency of increasing cardiac output on HR [8, 17,24].

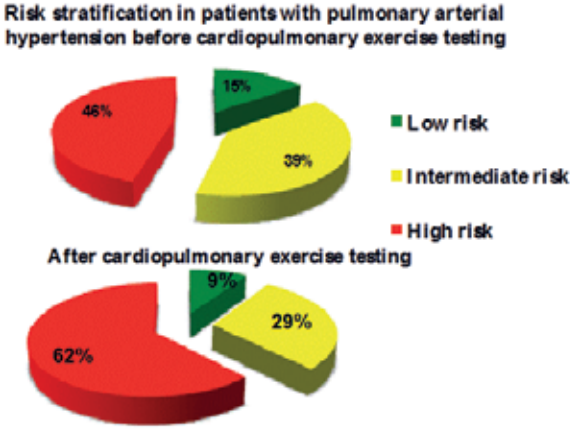

Figure 1. Risk stratification in PAH patients before and after CPET

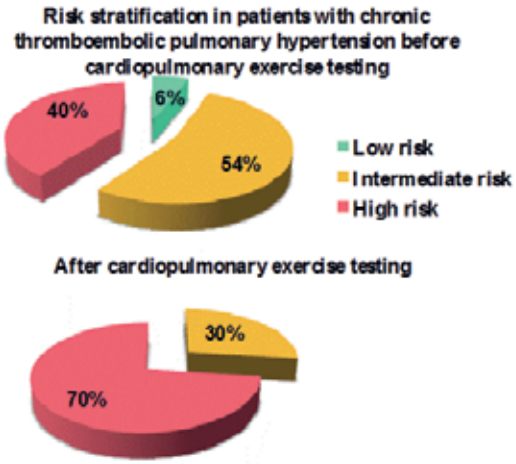

Figure 2. Risk stratification in CTEPH patients before and after CPET

Table 3. Typical cardiopulmonary exercise testing abnormalities in patients with PAH and CTEPH [23].

Parameters	PAH	CTEPH
Metabolic and cardiovascular		
Vo_2 peak	↓	↓
Vo_2 at AT	↓	↓
Vo_2/ work rate	↓	↓
O_2 pulse	↓	↓
Ventilation and mechanics		
VE peak	↓	↓
Breathing reserve	N	N
Gas exchange		
VE/Vco_2 slope	↑	↑↑
VE/Vco_2 at AT	↑	↑↑
$PetCo_2$	↓	↓↓
SaO_2	↓	↓↓
$P(a–ET)CO_2$	↑	↑↑
$P(A–a)O_2$	↑	↑↑
VD/VT	↑	↑↑

Vo_2 – oxygen intake; Vo_2 peak- oxygen intake at peak exercise; AT = anaerobic threshold; O_2 pulse = peak VO_2/ heart rate at peak exercise; VE – minute pulmonary ventilation; Vco_2- carbon dioxide output; VE/Vco_2 – ventilation equivalents slope; $P(A–a)O_2$ = alveolar–arterial oxygen pressure gradient at peak exercise; $P(a–ET)CO_2$=arterial–end-tidal carbon dioxide pressure gradient at peak exercise; $PETCO_2$ = end-tidal pressure of carbon dioxide; SaO_2 = arterial oxygen saturation as measured by pulse oximetry; WR= work rate; VD/VT - dead space ventilation.

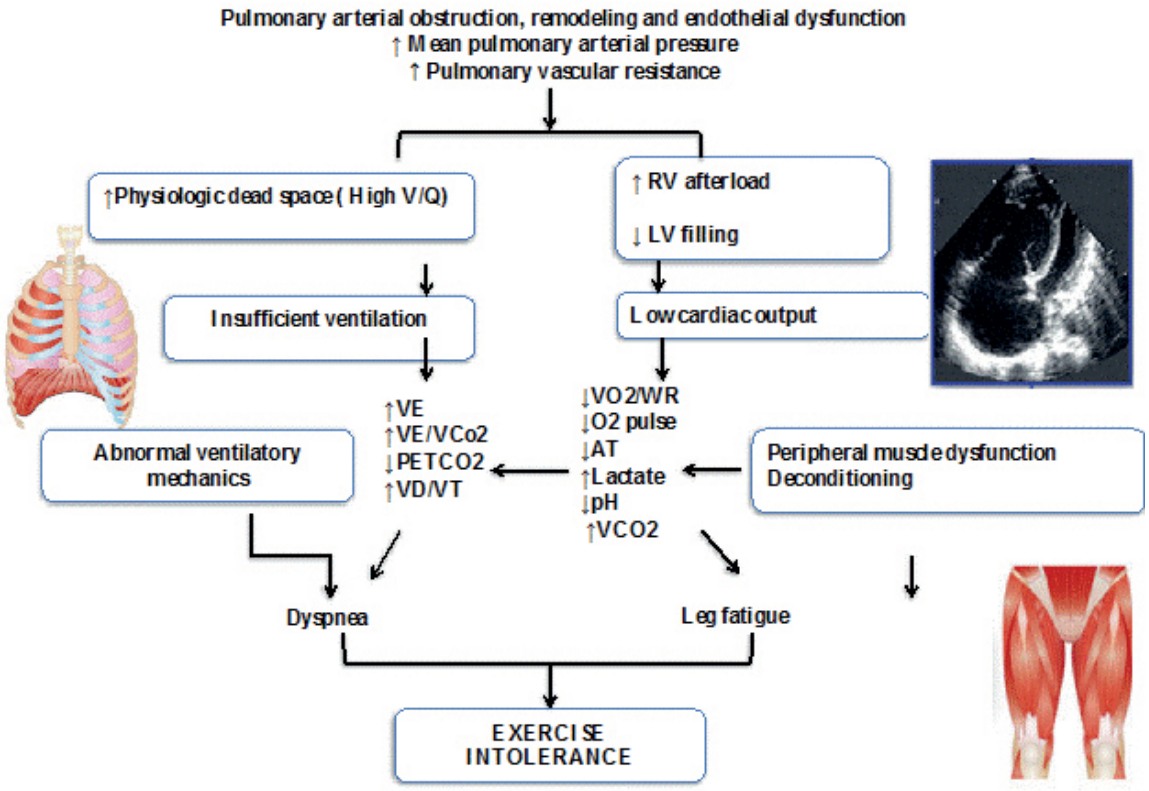

Figure 3. Pathophysiology and mechanisms of exercise intolerance in PAH and CTEPH patients.
Pathophysiology and mechanisms of exercise intolerance in pulmonary hypertension. Pulmonary vascular obstruction, remodeling, and endothelial dysfunction result in high ventilation–perfusion mismatching (V/Q) and impaired cardiac output. Inefficient ventilation proposes high ventilatory demand, high VE/V CO2 and VD/VT, and low end-tidal pressure of carbon dioxide (PETCO2). Cardiac limitation and peripheral muscle abnormalities result in a low anaerobic threshold, early-onset lactic acidosis (lactate), and increased VCO2, which provide further stimulation for excessive ventilation. Ventilatory mechanical constraints on VT expansion also contribute to dyspnea during exercise.

The arterial to end-tidal PCO2 gradient (P [a–ET] CO_2), a reflection of ventilation– perfusion inequality, is positive at rest and increases in patients with PAH and CTEPH, whereas in healthy individuals the P (a–ET) CO_2 decreases and is often negative at peak exercise [8, 25].

Thus, CPET is one of the reliable markers to reflect the progression of PAH and CTEPH. The CPET is necessary for pathogenic therapy efficacy assessment and for making decision of therapy escalation in patients with PAH, also as in CTEPH patients. The critical role of CPET in risk stratification in PAH and CTEPH patients should be emphasized.

CONCLUSION

The CPET results additionally to clinical and hemodynamic parameters demonstrated an importance in making decision on patients management strategy. The value of Vo_2 peak and VE / Vco2 slope reflected the risk of fatal events during 1 year, which was useful for resolving the issue about pathogenetic therapy volume, therapy escalation, the lasting time of lung transplantation and prognosis of patients with PAH and CTEPH.

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