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Cardiopulmonary exercise testing for treatment effect assessment in chronic thromboembolic pulmonary hypertension patients

Aim To determine possibilities of the cardiopulmonary stress test (CPST) as an unbiassed, noninvasive method for evaluation of the effect of managing patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Material and methods This study included 37 patients with CTEPH, 24 men (mean age, 53±15 years) and 13 women (mean age, 58±8.5 years). The diagnosis was verified and theCoperability was assessed according to 2015 European Society of Cardiology Clinical Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension (PH). The surgical treatment was used in 65% (n=24) of CTEPH patients: the group with pulmonary thromboendarterectomy constituted 35% (n=13); the group with balloon pulmonary angioplasty 30% (n=11); and the conservative tactics was used in 27% (n=10) of patients.

Results Baseline CPST parameters significantly correlated with parameters of right heart catheterization (RHC): mixed venous oxygen saturation (SvO_2) significantly positively correlated with $V'O_{2peak}$ (r=0.640, p<0.05), $V'O_{2/heart\ rate}$ (HR) (r=0.557; p<0.001), $PETCO_{2\ peak}$ (r=0.598, p<0.05), and $V'E/V'CO_2$ (r=0.587; p<0.001); cardiac output (CO) correlated with $V'O_{2/HR}$ (r=0.555, p<0.001), $PETCO_{2peak}$ (r=–0.476; p<0.05 and r=0.555, p<0.001 for $'E/V'CO_2$). In repeated testing, the physical working capacity ($V'O_{2peak}$) increased only in patients after the surgical treatment of CTEPH. Importantly in this process, significant correlations remained between a number of CPST and RHC parameters: SvO_2 correlated with $V'O_{2peak}$ (r=0.743; p<0.05), $V'O_{2/HR}$ (r=0.627; p<0.001), $PETCO_{2peak}$ (r=0.538; p<0.05), and $V'E/V'CO_2$ (r=0.597; p<0.001); $V'O_{2/HR}$, $PETCO_{2peak}$, and $V'E/V'CO_2$ significantly correlated with CO (r=0.645, p<0.001; r= –0.516, p<0.001, and r=0.555, p<0.001, respectively.

Conclusion CPST can be used as a noninvasive instrument for evaluation of the effect of CTEPH treatment, particularly in the absence of echocardiographic data for residual PH.

Keywords Pulmonary hypertension; chronic thromboembolic pulmonary hypertension; pulmonary thromboendarterectomy; balloon pulmonary angioplasty; cardiopulmonary stress test

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), a form of precapillary pulmonary hypertension (PH), is characterized by increased mean pulmonary artery (PA) pressure≥25 mm Hg combined with pulmonary capillary wedge pressure ≤15 mm Hg and pulmonary vascular resistance (PVR)>3 Wood units. In the contemporary classification, CTEPH, comprising a separate group of PH (group IV), is distinguished from most other forms of precapillary PH given its pathogenesis and the possibility of surgical treatment [1, 2]. CTEPH also represents a rare complication of acute pulmonary embolism (PE) and the most unfavorable variant of post-thrombotic syndrome in terms of a patient's life expectancy. Thus, the incidence of CTEPH in patients with a verified episode of PE ranges from 0.57% to 8.8% according to various authors, to give a mean of 3.4% [3–6]. Given the unfavorable prognosis of the disease and the affection of mainly working-age population (mean age of patients was from 46 to 49 years at the time of diagnosis verification), the development of this pathology is associated with serious social and economic implications [7, 8].

Early diagnosis of CTEPH is complicated by an insufficient introduction in practice of the algorithm for monitoring patients after PE, the medical community not being sensitive enough about the possible development of this disease, as well as the frequent absence of a

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temporal relationship between the clinical signs of CTEPH and PA thrombosis [9].

The most effective treatment for patients with CTEPH remains pulmonary thromboendarterectomy (TEE) under cardiopulmonary bypass and complete cessation of blood circulation. Due to improved surgical techniques and postoperative management applied by the world's leading CTEPH centers, three-year survival is achieved in 90% of patients [10]. However, according to the largest British registry, 51% of patients who were subjected to TEE have residual PH. Here, it should be noted that the mean PA pressure>38 mm Hg positively correlates with low long-term postoperative survival [11]. Transcatheter balloon pulmonary angioplasty (BPA), representing a relatively new method of surgical treatment for patients with CTEPH currently being widely introduced in clinical practice, is most effective for occlusion of segmental and sub-segmental pulmonary arteries [12–14]. Given the precapillary nature of PH and the formation of peripheral vasculopathy, the administration of specific pulmonary vasodilators is essential in treating patients with CTEPH. These can be useful in inoperable patients and patients with residual or recurrent PH after TEE [15].

After three to six months of the treatment, its efficacy in patients with CTEPH is assessed by studying patient's clinical and functional status and pulmonary hemodynamics registered during a right heart catheterization to confirm the presence of residual PH in order to determine further treatment tactics. Right heart catheterization representing an invasive intervention following surgical treatment of CTEPH requires patients to be hospitalized. Applying this procedure is also restricted due to economic factors; thus, its advisability with residual PH according to echocardiography is unlikely. Moreover, right heart catheterization cannot be used to assess the cardiovascular and respiratory reserve, whose increase and/or decrease is the most objective indicator of treatment efficacy. From this point of view, cardiopulmonary exercise testing (CPET) is the only non-invasive method for performing an objective assessment of changes of the reserve and the functional state of the cardiovascular and pulmonary systems during treatment in this category of patients.

Objective

To determine the possibilities of using CPET as an objective non-invasive technique for assessing treatment efficacy in patients with CTEPH using various methods.

Materials and methods

The study included 37 patients with CTEPH who were being treated in the V. A. Almazov National Medical Research Center in 2017–2020: 24 male patients (mean age 53 ± 15 years) and 13 female patients (mean age 58 ± 8.50 years). The study included patients with verified CTEPH following the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [2]. Age under 18 years was the exclusion criterion. The possibility of surgery was assessed; the treatment method was chosen by a multidisciplinary team, including a cardiologist, a cardiac surgeon, an interventional surgeon, and a radiologist. All patients signed informed consent prior to being included in the study. The study was carried out following the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki (developed originally in 1964 and amended in 2000). The study was performed withing the initiative research «Developing the risk stratification system for various forms of post-thrombotic syndrome» approved by the ethics committee of the V. A. Almazov National Medical Research Center (Minutes # No12–20 dated 21.12.2020). The follow-up period lasted from one to three years.

Echocardiography was performed using a VIVID 7 Dimension device. The right cardiac cavities were examined following the 2015 guidelines for echocardiography [16]. The right heart cavities were catheterized using a Swan-Ganz 7F thermodilution balloon catheter to evaluate hemodynamics by measuring mean right atrial pressure, systolic, diastolic, and mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output. PVR, stroke volume (SV), and cardiac index were calculated using the standard formulas.

All patients underwent complex pulmonary function tests (spirometry and body plethysmography) with standard and dynamic measurements; static lung volumes were measured using a VIASYS Healthcare Hoechberg system. Diffusion lung capacity for carbon monoxide (DLCO) was evaluated using a single breath and hold technique with adjustment for hemoglobin.

Serum levels of the N-terminal pro-brain natriuretic peptide (NT-proBNP) were determined by electrochemiluminescence using a standard Elecsys pack. Physical performance was evaluated by a 6 minute walk test (6MWT) following the American Thoracic Society guidelines [17].

CPET was conducted using an ergometer bicycle with a simultaneous estimation of gas exchange. Gas analysis used a breath-by-breath method (real-time analysis of each breath cycle) using an Oxycon Pro system. Patients performed symptom-limited exercise (RAMP) with continuously increasing load by 10 W/min on an ergometer bicycle. After recording an electrocardiogram (ECG), blood oxygen saturation

(SpO_2) was determined using a pulse oximeter continuously during the examination, with blood pressure (BP) being measured every 2 minutes. The patient's subjective sensations were assessed using a 10 point Borg score. The criteria for stopping exercise were the following: achieving the maximum possible individual load or the onset of symptoms that limit the exercise such as severe fatigue, dyspnea, presyncope, heart rhythm disorders, ischemic ECG abnormalities, retrosternal pain, or decreased BP. The response of the cardiovascular and pulmonary systems to exercise was assessed by the following indicators collectively: peak oxygen consumption ($V'O_{2\,peak}$); anaerobic threshold ($V'O_2$ at AT); increase in heart rate ($HR/V'O_2$) during exercise; oxygen pulse ($V'O_{2/HR}$); comprising SV index; partial pressure of carbon dioxide at the end of the exhalation ($PETCO_{2\,peak}$); ventilatory equivalent for CO_2 ($V'E/V'CO_2$), representing an integral indicator reflecting the effectiveness of minute ventilation; increase in oxygen consumption per work performed ($\Delta V'O_{2/\Delta W}$); blood oxygen saturation; BP at peak exercise. The value of $V'O_{2\,peak}$ ≥85% of the proper value (%P) and the level of anaerobic threshold ($V'O_2$ at AT) corresponding to 40–60% of $V'O_{2\,peak}$ were normal.

The data obtained were processed using SPSS Statistics 23.0. The quantitative indicators were expressed as the median [25th percentile; 75th percentile]; the categorical indicators were presented as the absolute and relative rates (n (%)). The quantitative variables in two independent samples were compared using the Mann-Whitney U-test. The Chi-squared test and Fisher's exact test were used to compare the categorical variables. The pairwise statistical relationships were identified using the Spearman correlation coefficient (r).

Results

Surgery was performed in 65% (n=24) of patients with CTEPH, including 35% (n=13) of patients after pulmonary TEE (Group 1) and 30% (n=11) of patients after BPA (Group 2). The efficacy of surgical treatment was evaluated 3–12 months after the surgery. Conservative treatment (Group 3) was used in 13 (35%) patients, three of whom refused the suggested surgery, despite it not being contraindicated to them. Thus, the group of inoperable patients (due to the morphology of LA lesion or comorbidities) accounted for only 27% (n=10). The efficacy of drug therapy was estimated in this category of patients after 12 months. All patients underwent CPET at baseline; the procedure was repeated in 46% (n=17) of patients according to the schedule of surgical intervention. It should be noted that patients with CTEPH functional class (FC) IV were not included in this study as they were not able to perform exercise testing before surgery.

Clinical characteristics of patients included in the study are provided in Table 1. Patients selected for different surgeries did not differ in terms of their functional status and hemodynamic findings, both between the two surgical treatment groups and when compared with the conservative tactics group (see Table 1). It should be noted that 75% (n=26) of patients had CTEPH FC III at the time of assessing the possibility of surgical treatment, which is their condition was severe. Thus, the problem of early diagnosis of CTEPH is relevant. The analysis of the CPET indicators in all groups showed a significant decrease in the cardiovascular and respiratory reserves – specifically, reduced peak oxygen consumption ($V'O_{2\,peak}$) and high ventilatory equivalent for carbon dioxide ($V'E/V'CO_{2\,peak}$) at peak exercise. SpO_2 was significantly lower at peak exercise in patients selected for pulmonary TEE than patients selected for BPA, 87 [83; 91] % and 93 [92; 94] %, respectively ($p=0.014$). At the same time, the indicator of pulmonary hemodynamics PVR, which is typically used to characterized the condition of the cardiovascular system, was lower in patients with proximal lesions (Group 1) than in patients with distal lesions (Group 2; $p=0.037$). This is probably due to the peculiarities of selecting patients in our center, such as PVR>1200 dyn s/cm-5 being regarded as a relative contraindication to pulmonary TEE given the high risk of perioperative adverse events: postoperative residual PH and pulmonary reperfusion lesions and/or refractory right ventricular failure.

The analysis of the baseline findings of CPET and the invasive assessment of pulmonary hemodynamics showed statistically significant relationships of some indicators. SvO_2 was positively correlated with $V'O_{2\,peak}$ ($r=0.640$; $p<0.05$), $V'O_{2/HR}$ ($r=0.557$; $p<0.001$), $PETCO_{2\,peak}$ ($r=0.598$; $p<0.05$) and $V'E/V'CO_2$ ($r=0.587$; $p<0.001$). Such CPET indicators as $V'O_{2/HR}$, $PETCO_{2\,peak}$ and $V'E/V'CO_2$ were statistically significantly correlated with the important prognostic parameter CO: $r=0.555$; $p<0.001$ for $V'O_{2/HR}$, $r=-0.476$; $p<0.05$ for $PETCO_{2\,peak}$, and $r=0.555$; $p<0.001$ for $V'E/V'CO_2$. At the same time, there was a negative correlation between $V'O_{2/HR}$ and PVR ($r=-0.501$; $p<0.05$).

Drug therapy for most examined patients included diuretics (30%) and specific therapy for pulmonary hypertension (73%), which was ordered in the surgical treatment group only to patients with CTEPH FC III–IV. At the same time, a combined, off-label specific therapy of PH was used in 30% of patients, which further suggests the severity of baseline condition of the patients.

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Table 1. Baseline clinical characteristics of patients with chronic thromboembolic pulmonary hypertension

Parameter	Group 1 (TEE, n=13)	Group 2 (BPA, n=11)	Group 3 (conservative treatment, n=13)	p
Age, years	53 [38; 64]	54 [45; 64]	58 [53; 71]	0.321
Female, %	15	38	55	0.180
FC I/II/III, n	0/6/7	0/5/6	0/4/9	0.085
6MWT distance, m	346 [236; 434]	408 [380; 455]	380 [275; 401]	0.120
NT-proBNP, pg/mL	1234 [305; 2238]	511 [283; 2666]	1671 [567; 2041]	0.435
DLco, %	68 [55; 86]	67 [52; 79]	66 [61; 78]	0.351
Cardiopulmonary exercise testing findings				
$V'O_{2\,peak}$, mL/min/kg	13.6 [12.5; 20.7]	14.0 [11.1; 15.3]	13.7 [11.6; 17.3]	0.384
SpO_2, % (N >95%)	87 [83; 91]	93 [92; 94]	92 [87; 95]	$p_{1\text{-}3}$=0.014 $p_{1\text{-}2}$=0.052 $p_{2\text{-}3}$=0.678
$V'O_2$/HR, mL/beat	2.7 [1.9; 3.5]	2.6 [2.4; 3.2]	2.4 [2.1; 3.1]	0.951
$PETCO_{2\,peak}$, mm Hg (N 2–5 mm Hg)	52.3 [41.1; 70.0]	56.8 [45.4; 60.4]	55.6 [48.1; 71.2]	0.865
$V'E/V'CO_{2\,peak}$ (N 32–34)	10.2 [7.0; 11.6]	10.9 [9.2; 12.9]	9.3 [7.7; 12.8]	0.530
$HR/VO_{2\,slope}$, beats/mL/kg (N 4–6 beats/mL/kg)	10.9 [7.7; 14.5]	10.9 [9.9; 13.2]	12.8 [11.4; 14.9]	0.849
$V'O_{2\,peak}$ at, mL/min/kg	9.2 [7.4; 10.5]	9.7 [7.5; 11.3]	9.0 [7.3; 10.7]	0.868
$\Delta V'O_{2/\Delta W}$ (N 8.5–11 mL/min/W)	9,2 [7,4; 10,5]	9,7 [7,5; 11,3]	9,0 [7,3; 10,7]	0,868
Echocardiographic findings				
RA area, cm^2	28 [22; 35]	25 [22; 38]	31 [26; 37]	0.321
Parasternal RV dimension, mm	36 [33; 41]	36 [33; 43]	38 [36; 48]	0.671
Basal RV dimension, mm	50 [42; 62]	47 [44; 57]	42 [44; 59]	0.851
RV/LV	1.3 [1.2; 1.5]	1.3 [1.2; 1.4]	1.2 [1.20; 1.53]	0.652
TAPSE, mm	16 [12; 17]	16 [13; 18]	17 [14; 19]	0.123
Estimated PA systolic pressure, mm Hg	65 [41; 73]	57 [37; 67]	55 [40; 66]	0.423
Right heart catheterization findings				
Mean PA pressure, mm Hg	54 [45; 67]	58 [50; 63]	51 [44; 57]	0.652
CVP, mm Hg	14 [12; 15]	12 [7; 20]	11 [5; 17]	0.543
CO, L/min	4.5 [3.7; 5.7]	3.5 [2.8; 4.5]	3.71 [2.9; 4.4]	$p_{1\text{–}2}$=0.021
CI	2.2 [1.7; 2.6]	1.8 [1.6; 2.2]	2.0 [3.0; 4.3]	0.861
PVR, dyn·s/cm^{-5}	800 [510; 854]	1160 [850; 1324]	918 [696; 1105]	$p_{1\text{–}2}$=0.037
SvO_2, %	63 [55; 66]	60 [55; 66]	59 [53; 65]	0.117

The data are presented as Me [25th percentile; 75th percentile] if not otherwise specified. TEE – thromboendarterectomy; BPA – balloon pulmonary angioplasty; FC – functional class; 6MWT – 6-minute walking test; NT-proBNP – N-terminal pro-brain natriuretic peptide; HR – heart rate; RA – right atrium; RV – right ventricle; LV – left ventricle; RV:LV – the ratio of right and left ventricular basal dimensions; TAPSE – tricuspid annular plane systolic excursion; PBP – pulmonary blood pressure; CVP – central venous pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance; SvO_2 – oxygen saturation of mixed venous blood.

Table 2 summarizes changes in clinical findings according to the treatment administered. The TEE and BPA groups showed higher efficacy compared to the conservative treatment tactics. There were no patients with CTEPH FC III in Group 1 and Group 2 after surgery and 46% of patients had CTEPH FC III in Group 3, which also included 3 patients with CTEPH FC IV (χ^2=8.75; p=0.001). The results of 6MWT showed a significant improvement in the functional performance of patients after surgery: +151 m in the TEE group and +105 m in the BPA group compared to +13 m in the drug treatment group (p=0.002), as well as beneficial changes in the serum levels of NT-proBNP: a decrease of 1087 pg/mL and 433 pg/mL in the TEE and BPA groups, respectively, along with an increase of 439 pg/mL in the levels of NT-proBNP in the conservative tactics group.

In both groups of surgical treatment, reverse remodeling of the right heart cavities was observed as well as the improvement of the contractile function of the right ventricle (RV) as compared with a group of inoperable patients with predominantly negative changes such as dilatation of the right heart cavities ($p<0.05$). According to the echocardiographic findings, more pronounced beneficial changes were detected in the pulmonary TEE group. Following surgery, there was a decrease in the right atrial area (ΔSRA=–9 cm^2), RV

Table 2. Clinical characteristics of patients with chronic thromboembolic pulmonary hypertension after treatment

Parameter	Group 1 (TEE, n=13)	Group 2 (BPA, n=11)	Group 3 (conservative treatment, n=13)	p
FC I/II/III/IV, n	7/4/0/0	7/4/0/0	0/4/6/3	p_{1-3}=0.001 p_{2-3}=0.001
6MWT distance, m	497 [470; 561]	513 [503; 547]	393 [291; 461]	p_{1-3}=0.002 p_{2-3}=0.003
NT-proBNP, pg/mL	147 [102; 254]	68 [45; 234]	1232 [326; 4308]	p_{1-3}=0.005 p_{2-3}=0.047 p_{1-2}=0.201
Echocardiographic findings				
RA area, cm^2	19 [18; 22]	22 [17; 24]	30 [24; 36]	p_{1-3}<0.05 p_{2-3}<0.05
Parasternal RV dimension, mm	32 [30; 37]	34 [33; 35]	41 [36; 45]	p_{1-3}<0.05 p_{2-3}<0.05
Basal RV dimension, mm	41 [38; 45]	43 [38; 43]	51 [43; 59]	p_{1-3}<0.05 p_{2-3}<0.05
RV/LV	1.0 [0.9; 1.1]	0.9 [0.8; 1.0]	1.3 [1.1; 1.3]	p_{1-3}<0.05 p_{2-3}<0.05
TAPSE, mm	20 [17; 22]	19 [18; 23]	14 [14; 16]	p_{1-3}<0.05 p_{2-3}<0.05
Right heart catheterization findings				
Mean PA pressure, mm Hg	25 [24; 27]	35 [30; 40]	52 [43; 66]	p_{1-3}=0.001 p_{2-3}=0.001 p_{1-2}=0.010
CVP, mm Hg	10 [6; 12]	11 [8; 12]	10 [7; 18]	0.452
CO, L/min	5.2 [4.5; 6.1]	5.8 [4.6; 6.3]	4.4 [3.6; 5.6]	p_{1-2}=0.106
CI	2.5 [2.4; 3.0]	2.8 [2.6; 3.7]	2.3 [1.9; 2.4]	p_{1-2}=0.179 p_{1-3}=0.223 p_{2-3}=0.017
PVR, dyn·s/cm^{-5}	245 [160; 290]	276 [240; 512]	1048 [712; 1754]	p_{1-3}=0.001 p_{2-3}=0.001 p_{1-2}=0.051
SvO_2, %	70 [64; 71]	74 [69; 76]	62 [58; 64]	p_{1-3}=0.001 p_{2-3}=0.001 p_{1-2}=0.047

The data are presented as Me [25th percentile; 75th percentile] if not otherwise specified. TEE – thromboendarterectomy; BPA – balloon pulmonary angioplasty; FC – functional class; 6MWT – 6-minute walking test; NT-proBNP – N-terminal pro-brain natriuretic peptide; RA – right atrium; RV – right ventricle; LV – left ventricle; RV:LV – the ratio of right and left ventricular basal dimensions; TAPSE – tricuspid annular plane systolic excursion; PBP – pulmonary blood pressure; CVP – central venous pressure; CO – cardiac output; CI – cardiac index; PVR – pulmonary vascular resistance; SvO_2 – oxygen saturation of mixed venous blood.

dimensions (ΔRVpar=–4 mm and ΔRVbas=–9 mm), and the ratio of the right and left ventricular dimensions ΔRV:LV=–0.4; increased ΔTAPSE=4 mm. Patients subjected to stage BPA had the following changes of the echocardiographic indicators: ΔSRA=–3 cm^2; ΔRVpar=–2 mm; ΔRVbas=–4 mm; ΔRV:LV=–0.4; ΔTAPSE=3 mm. However, the differences between different treatment groups were statistically insignificant. The trend to more severe reverse remodeling of the heart cavities in the case of TEE compared to BPA can be explained in terms of more favorable main hemodynamic indicators. Mean RA pressure and PVR in patients after TEE, compared with patients after BPA, were 25 [24; 27] mm Hg versus 35 [30; 40] mm Hg (p=0.017) and 245 [160; 290] dyn s/cm – 5 versus 276 [240; 512] dyn·s/cm – 5 (p=0.051), respectively. According to the strict residual PH criteria (mean PA pressure >25 mm Hg and PVR >240 dyn·s/cm – 5) used in our center, this was found in 50% of patients after surgery, indicating ordering/extending specific PH treatment. Vasodilators were canceled in 12 (50%) patients due to the normalization of all pulmonary hemodynamic parameters.

Table 3 shows that physical performance ($V'O_{2\ peak}$), which is determined by the cardiovascular and pulmonary reserves, increased only in patients subjected to CTEPH. This parameter was significantly higher in the BPA group than in the conservative tactics group (p=0.02). Moreover,

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Table 3. Changes in the cardiopulmonary exercise test measurements depending on the treatment of patients with chronic thromboembolic pulmonary hypertension

Parameter	Group 1 (TEE, n=13)	Group 2 (BPA, n=11)	Group 3 (conservative treatment, n=13)	p
ΔSpO_2, %	6.5 [5.3; 7.8]	–2.0 [–4.0; 1.5]	–0.1 [–1.75; 1.00]	p_{1-3}=0.001 p_{1-2}=0.001 p_{2-3}=0.268
$\Delta V'O_{2\,peak}$, mL/min/kg	3.6 [–0.5; 12.5]	5.0 [3.6; 6.9]	0.4 [–2.4; 1.2]	p_{1-2}=0.858 p_{1-3}=0.141 p_{2-3}=0.020
$\Delta V'O_{2/HR}$, mL/beat	1.2 [–2.1; 7.8]	2.8 [1.7; 3.9]	–0.1 [–1.3; 1.7]	p_{1-2}=0.274 p_{2-3}=0.028 p_{1-3}=0.455
$\Delta HR/VO_{2\,slope}$, beats/mL/kg	–2.2 [–5.7; 1.2]	–3.4 [–4.5; – 2.1]	–0.3 [–0.6; 1.3]	p_{1-2}=0.347 p_{1-3}=0.272 p_{2-3}=0.020
$\Delta PETCO_{2\,peak}$, mm Hg	1.0 [1.0; 1.0]	0.72 [0.6; 1.1]	0.0 [–0.1; 0.4]	p_{1-2}=0.625 p_{2-3}=0.007 p_{1-3}=0.018
$\Delta V'E/V'CO_{2\,peak}$	–6.2 [–19.0; –6.2]	–10.9 [–16.9; –8.1]	2.3 [–1.3; 3.9]	p_{1-2}=0.186 p_{1-3}=0.392 p_{2-3}=0.001
$\Delta V'O_{2\,peak}$ at AT, mL/min/kg	3.0 [–0.3; 3.0]	3.3 [2.5; 47.0]	–1.8 [–7.4; 0.0]	p_{1-2}=0.628 p_{1-3}=0.115 p_{2-3}=0.004

The data are expressed as Me [25th percentile; 75th percentile]. TEE – thromboendarterectomy; BPA – balloon pulmonary angioplasty; SpO_2 – blood oxygen saturation determined by pulse oximetry; $V'O_{2\,peak}$ – peak oxygen consumption; HR – heart rate; $V'O_{2/HR}$ – oxygen pulse; $HR/VO_{2\,slope}$ – the increase in HR per oxygen volume during exercise; $PETCO_{2\,peak}$ – partial pressure of carbon dioxide at the end of the exhalation at peak exercise; $V'E/V'CO_{2\,peak}$ – fan equivalent of carbon dioxide at peak exercise; $V'O_2$ at AT – oxygen consumption at anaerobic threshold.

an increase in oxygen pulse ($V'O_{2/HR}$), representing the equivalent of stroke volume, was higher in the BPA group; moreover, ventilatory equivalent for carbon dioxide $V'E/V'CO_2$ decreased compared to that in inoperable patients, i.e., the delivery of oxygen per work performed improved due to the recovery of lung perfusion; as a result, cardiac performance and pulmonary gas exchange were normalized. There were no statistically significant differences in CPET indicators between the different surgery groups. At the same time, it is essential that statistically significant relationships of several indicators of CPET and right heart catheterization be sustained over time following surgical treatment of CTEPH. Oxygen saturation of the mixed venous blood was positively correlated with $V'O_{2\,peak}$ ($r=0.743$; $p<0.05$), $V'O_{2/HR}$ ($r=0.627$; $p<0.001$), $PETCO_{2\,peak}$ ($r=0.538$; $p<0.05$) and $V'E/V'CO_2$ ($r=0.597$; $p<0.001$). Some indicators, such as $V'O_2/HR$, $PETCO_{2\,peak}$, and $V'E/V'CO_{2\,peak}$, were statistically significantly correlated with CO, $r=0.645$, $p<0.001$; $r=-0.516$, $p<0.001$, and $r=0.555$, $p<0.001$, respectively. Oxygen pulse ($V'O_{2/HR}$) remained negatively correlated with PVR ($r=-0.543$; $p<0.05$).

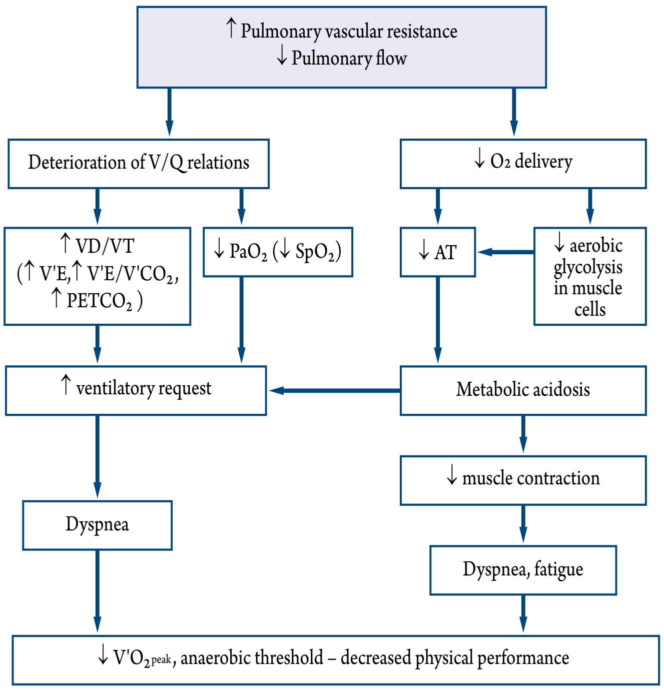
Discussion

The primary criterion for efficacy of treatment of CTEPH patients is an increase in the cardiovascular and pulmonary reserves, which consists in improved physical performance, as well as an improvement in the patient's subjective state and pulmonary hemodynamics. Although the simple and affordable 6MWT procedure is widely used in clinical practice to assess physical performance, it has significant limitations due to the influence of anthropometric indicators, age, and the patient's motivation to achieve the test results [18, 19]. Therefore, CPET has been increasingly used as the most accurate and objective method of assessing the cardiovascular and pulmonary reserves. During CPET with increasing exercise load, oxygen consumption and carbon dioxide emission are determined in real time using a gas analyzer to assess oxygen delivery and utilization in the patient's body [20]. Violated oxygen delivery is the main mechanism for reduced levels of physical performance in patients with CTEPH. The pathogenesis of CTEPH is based on incomplete recanalization and fibrous transformation of thrombotic masses, along with the obliteration of pulmonary arteries and the development of peripheral vasculopathies of varying severity. This contributes to the progression of PH even in the absence of recurrent thromboembolic events. As with other forms of PH, the most likely outcomes of the disease are severe pancreatic dysfunction and heart failure.

Fig. 1 shows the main mechanisms of oxygen delivery impairment in patients with CTEPH. Obliteration of the pulmonary arteries and high PVR prevent an adequate increase in pulmonary flow with increasing exercise load, which leads to RV overload and worsening of ventilation-perfusion ratios due to reduced perfusion. The lack of a sufficient increase in diffusion area and a decrease in the time of erythrocyte run in the pulmonary circulation reduces the diffusion capacity of the alveolar-capillary membrane as exercise load increases, along with progressive hypoxemia and deterioration of pulmonary gas exchange, which is characterized by increase dead space ventilation [21]. Low-efficacy hyperventilation develops to compensate these disturbances, as evidenced by the increased ventilatory equivalent for carbon dioxide and a sharp decrease in partial pressure of carbon dioxide at the end of the exhalation. These changes manifest in dyspnea. Increasing hypoxemia results in a decrease of the aerobic formation of macroergs in the skeletal muscle mitochondria, early overlay of anaerobic glycolysis, which is characterized by a decreased anaerobic threshold and reduced exercise tolerance. As PH increases, the return of blood to the left heart cavities decreases. The compression of the left ventricle by enlarged right cavities is also a contributing factor, which ultimately decreases CO because SV cannot increase adequately. According to CPET, this is manifested by changes in oxygen pulse, which serves as an index of SV. Thus, reduced oxygen delivery in patients with CTEPH is due to impaired pulmonary and cardiac function, which is supported by a decrease in oxygen delivery per work performed ($V'O_{2/W}$).

The analysis of the baseline CPET indicators of all examined patients with CTEPH revealed a significant decrease in the cardiovascular and pulmonary reserves characterized by a decrease in peak oxygen consumption: mean $V'O_{2\ peak}$ was 13.8 [11.1; 20.7] mL/min/kg. CO increased during exercise mainly due to the accelerated increase in HR (mean $HR/VO_{2\ slope}$ was 10.2 [7.0; 12.9] beats/mL/kg), since the increase in oxygen pulse (SV index) was insignificant (mean $V'O_{2/HR}$ was 8.0 [4.8; 11.6] mL/beat). Severe hyperventilation and high ventilatory equivalent for carbon dioxide (mean $V'E/V'CO_2$ was 54.9 [41.1; 71.2]) at peak exercise indicated impaired ventilation-perfusion ratios typical of patients with CTEPH. More pronounced desaturation in CPET in patients selected for pulmonary TEE as compared to patients selected for BPA is probably due to massive post-thrombotic injury of the pulmonary arteries, including both main and peripheral branches, which leads to more severe impairment of ventilation-perfusion ratios and hypoxemia. The detected correlations of such important indicators of the right heart catheterization as oxygen saturation of mixed venous blood and CO with the CPET indicators are of obvious interest: $V'O_{2\ peak}$, $V'O_{2/HR}$, $PETCO_{2\ peak}$, and $V'E/V'CO_2$. This confirms the diagnostic and prognostic value of the non-invasive assessment of the condition of the cardiopulmonary system.

Figures 1. Figure 1. Pathogenesis of impaired oxygen delivery in patients with chronic thromboembolic pulmonary hypertension



AT – anaerobic threshold; Vd/Vt – dead space ventilation; PaO2 – partial pressure of oxygen at the end of the exhalation; $V'O_{2\ peak}$ – peak oxygen consumption.

The analysis of the post-operative CPET findings showed decrease severity of hyperventilation and $V'E/V'CO_2$, as well as an increase in $PETCO_{2\ peak}$, which indicated improved ventilation-perfusion ratios, resulting in an increase in $V'O_{2\ peak}$ and the anaerobic threshold. There was also a normalization of the CO growth structure due to an adequate increase in the left ventricular stroke volume (Fig. 2).

Thus, unlike in conservatively treated patients, cardiovascular and pulmonary reserves increased following surgery in patients with CTEPH. These results correspond to the foreign literature data, which demonstrate the high efficacy of surgical methods of treatment for CTEPH [22–24]. The absence of statistically significant differences in the CPET indicators in the different surgery groups with clearly greater efficacy of pulmonary TEE is probably due to the small sample size used in our study. At the same time, it is important that statistically significant relations

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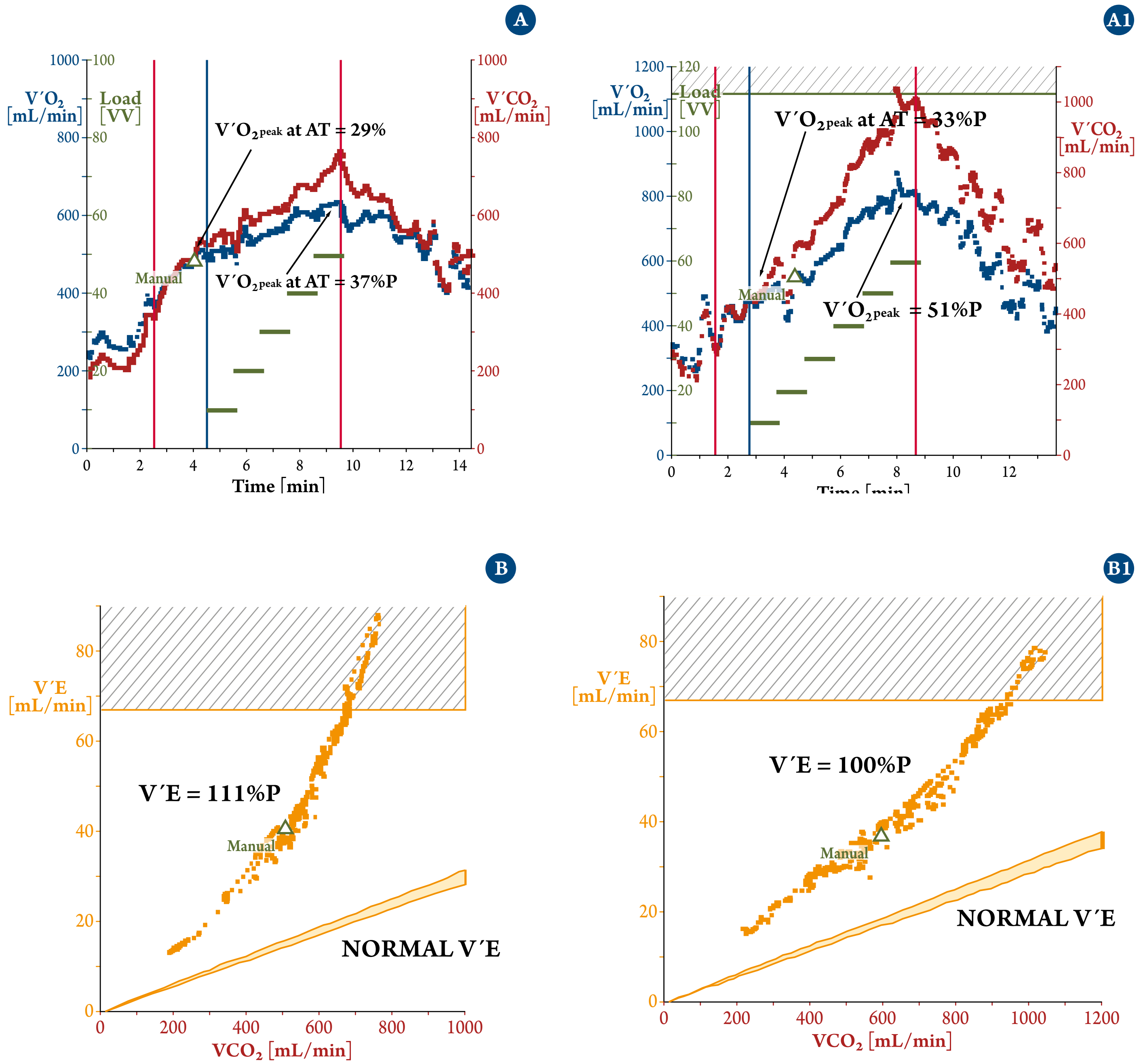
Figures 2. Changes in CPET indicators in patients with CTEPH after surgery



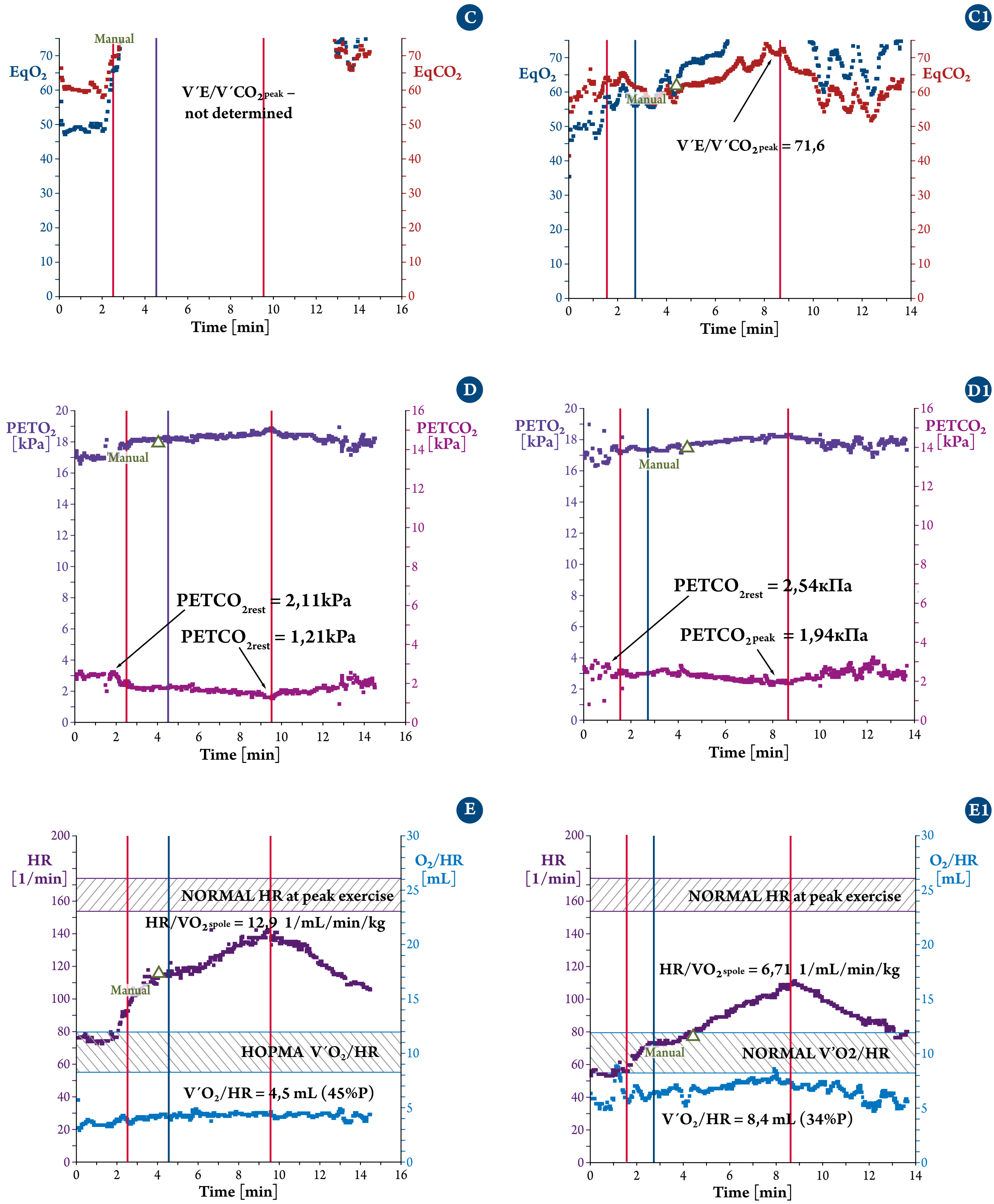
A-E – before surgery; A1-E1 – after surgery; VO_2 at AT – oxygen consumption at anaerobic threshold; P – proper value; $V'O_{2\,peak}$ – peak oxygen consumption; V´E – ventilation volume; $V'E/V'CO_{2\,peak}$ – ventilatory equivalent of carbon dioxide at peak exercise; $PETCO_{2\,rest}$ – partial pressure of carbon dioxide at the end of exhalation at rest; $PETCO_{2\,peak}$ – partial pressure of carbon dioxide in the end of exhalation at peak exercise; HR – heart rate; $V'O_{2/HR}$ – oxygen pulse; $HR/VO_{2\,slope}$ –increase in heart rate per oxygen volume during exercise

of the integral CPET indicators ($V'O_{2\,peak}$, $PETCO_{2\,peak}$, $V'E/V'CO_2$) with the indicators of right heart catheterization important for risk stratification, such as oxygen saturation of mixed venous blood and CO, continue after surgery for CTEPH. Thus, we suggest that CPET can be used as a non-invasive method for assessing the efficacy of surgical treatment of patients with CTEPH, both in combination with right heart catheterization to optimize risk stratification in patients with residual PH, and independently in patients unlikely to have residual PH according to echocardiographic findings.

Conclusion

Cardiopulmonary exercise testing can be effectively used as an essential tool for stratifying the risk of adverse outcomes in patients with pulmonary hypertension to assess the efficacy of surgery for chronic thromboembolic pulmonary hypertension. In future, in order to favorably balance the risk-benefit ratio, it would be reasonable to

Figure 2 (continued). Changes in CPET indicators in patients with CTEPH after surgery



A-E – before surgery; A1-E1 – after surgery; VO_2 at AT – oxygen consumption at anaerobic threshold; P – proper value; $V'O_{2\,peak}$ – peak oxygen consumption; V´E – ventilation volume; $V'E/V'CO_{2\,peak}$ – ventilatory equivalent of carbon dioxide at peak exercise; $PETCO_{2\,rest}$ – partial pressure of carbon dioxide at the end of exhalation at rest; $PETCO_{2\,peak}$ – partial pressure of carbon dioxide in the end of exhalation at peak exercise; HR – heart rate; $V'O_{2/HR}$ – oxygen pulse; $HR/VO_{2\,slope}$ –increase in heart rate per oxygen volume during exercise.

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assess the feasibility of using this non-invasive method as the treatment of choice in patients who are unlikely to have residual pulmonary hypertension according to echocardiography.

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