Cardiopulmonary Exercise Testing to Detect Chronic Thromboembolic Pulmonary Hypertension in Patients with Normal Echocardiography

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Key Words

Cardiopulmonary exercise testing · Chronic thromboembolic pulmonary hypertension · Echocardiography · Pulmonary artery pressure · Pulmonary circulation · Pulmonary embolism · Pulmonary hypertension

Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of pulmonary embolism (PE). Taking into account the reported incidence of CTEPH after acute PE, the number of patients with undiagnosed CTEPH may be high. **Objectives:** We aimed to determine if cardiopulmonary exercise testing (CPET) could serve as complementary tool in the diagnosis of CTEPH and can detect CTEPH in patients with normal echocardiography. **Methods:** At diagnosis, we analyzed the data of CPET parameters in 42 patients with proven CTEPH and 51 controls, and evaluated the performance of two scores. **Results:** VE/VCO_2 slope, EQO_2 , $EQCO_2$, $P(A-a)O_2$, end-tidal partial pressure of CO_2 at anaerobic threshold ($PETCO_2$) and capillary to end-tidal carbon dioxide gradient [$P(c-ET)CO_2$] were significantly different between patients with CTEPH and controls ($p < 0.001$). $P(c-$

$ET)CO_2$ was the single parameter with the highest sensitivity (85.7%) and specificity (88.2%). A score combining VE/VCO_2 slope, $P(A-a)O_2$, $P(c-ET)CO_2$, $PETCO_2$ [4-parameter-CPET (4-P-CPET) score] reached a sensitivity of 83.3% and a specificity of 92.2% after cross-validation. In 42 patients with CTEPH, echocardiography identified PH in 29 patients (69%), but it was normal in 13 patients (31%). All patients with normal or unmeasurable right ventricular systolic pressure had a pathological CPET. Twelve of the 13 patients (92%) were detected by both CPET scores. **Conclusion:** CPET is a useful noninvasive diagnostic tool for the detection of CTEPH in patients with suspected PH but normal echocardiography. The 4-P-CPET score provides a high sensitivity with the highest specificity.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious sequelae of pulmonary embolism (PE). The reported incidence of CTEPH after acute symp-

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tomatic PE is highly variable, ranging from 0.8% [1] to 8.8% [2]. This variability might depend on the screening approaches applied, e.g. the search for CTEPH in all patients with previous PE or the study of symptomatic patients only. Additionally, it might be different between patients with just one previous PE episode and patients with a history of recurrent thromboembolism [3]. Pengo et al. [4] reported an incidence of 3.8%. Taking into account an overall incidence of PE of 0.6–1.45/1,000 person-years [5–7] and that 20–52% of patients with CTEPH are not aware of symptomatic episodes of acute PE [8–11], a high number of patients with CTEPH remain undiagnosed. When pulmonary hypertension (PH) is suspected, the guidelines recommend echocardiography as the first diagnostic step [12, 13]. If the echocardiogram is suspicious for PH, left heart disease, pulmonary disease and ventilatory disorders should be ruled out [12, 13]. In patients in whom signs of CTEPH are not detectable by CT scan, a ventilation/perfusion scan is mandatory to exclude or confirm CTEPH [12, 14]. Right heart catheterization is required to establish a firm diagnosis of PH [12].

Noninvasive estimation of systolic pulmonary artery pressure (PAP) is feasible in the majority of patients [15–17]. The criteria for normal pressure are defined as tricuspid regurgitation peak velocity <2.8 m/s and peak systolic pressure <36 mm Hg [15]. However, echocardiography might underestimate PAP in mild PH [13, 18, 19]. In patients with concomitant pulmonary disease, false-negative and false-positive results may occur [20]. Echocardiography could even fail to detect CTEPH at an early stage.

In CTEPH, vascular obstruction leads to decreased blood flow followed by increased dead space ventilation [21]. This results in an increased (arterial or) capillary to end-tidal carbon dioxide gradient [$P(c\text{-ET})\text{CO}_2$] [21]. Recently, Scheidl et al. [21] reported that the $P(c\text{-ET})\text{CO}_2$ gradient can be a helpful diagnostic tool to discriminate between CTEPH and pulmonary arterial hypertension (PAH). Dumitrescu et al. [22] studied parameters of cardiopulmonary exercise testing (CPET) in patients with scleroderma and found that a high VE/VCO_2 ratio and decreasing end-tidal partial pressure of CO_2 at anaerobic threshold (PETCO_2) identifies the presence of pulmonary vasculopathy. Armstrong et al. [23] showed that CPET can help to detect PH in patients with interstitial lung disease.

We aimed to determine the role of CPET as a complementary tool in the diagnostic process for CTEPH and whether CPET will detect PH in patients with suspected CTEPH but normal echocardiographic findings.

Methods

For the retrospective analysis, we recruited 62 consecutive patients referred to the Mission Medical Hospital with suspected CTEPH due to exertional dyspnea and intravascular mass or mismatched perfusion abnormalities in ventilation-perfusion scans between January 2010 and April 2013.

In order to confirm or exclude CTEPH, the patients underwent a diagnostic workup according to international guidelines [12, 14]. Echocardiography (Vivid7[®], GE Medical Systems, Solingen, Germany) was performed. Body plethysmography (Masterscreen Body/Diff[®]; CareFusion, Hoechberg, Germany) was conducted according to the European Respiratory Society statement [24]. Computed tomography (Activion 16[®]; Toshiba Medical Systems, Neuss, Germany) and ventilation-perfusion scans (Technegas-Generator[®]; Tetley Medical Limited, Lucas Heights, N.S.W., Australia; E Cam Variable[®]; Siemens Medical Solutions Inc., Hoffman Estates, Ill., USA) were conducted to confirm or exclude chronic thromboembolism. Right heart catheterization was performed according to previous guidelines using a Swan-Ganz catheter (Smith Medical, Grasbrunn, Germany) [12]. Measurements were conducted with the monitor system [IntelliVue MP70 (M8007A)[®]; Philips Medizinsysteme, Böblingen, Germany]. Pulmonary angiography (Integris Allura; Philips Medical Systems, Best, The Netherlands: films stored digitally) was performed to assess operability and/or confirm diagnosis at the University Hospital Homburg/Saar. Diagnosis and treatment strategy were discussed by an interdisciplinary CTEPH team. Capillary blood gases were taken from the ear and measured at rest and at peak exercise (ABL 800 Basic[®]; Radiometer, Cadolzburg, Germany).

CPET (Masterscreen CPX[®], CareFusion; E-bike basic PC plus; GE Medical Systems) was performed at diagnosis according to the American Thoracic Society and American College of Chest Physicians statement, as recently described [25, 26]. It included a 2-min registration at rest and a 2-min recording of unloaded pedaling. The following exercise protocol consisted of an increasing workload of 25 W/2 min per ramp. Exercise was terminated when withdrawal criteria were met or by symptom limitation. Expiratory fraction of O_2 and CO_2 , respiratory rate and minute ventilation were measured breath by breath. Temperature and air pressure were recorded continuously. The anaerobic threshold (AT) was determined at EQO_2 nadir.

Seventeen patients were excluded due to incomplete data. For the final data analysis, only patients were selected who had proven CTEPH following an anticoagulation of at least 3 months and met the following hemodynamic criteria: mean PAP (mPAP) at rest >25 mm Hg or mPAP at exercise >30 mm Hg if mPAP at rest was <25 mm Hg. Forty-two individuals fulfilled these criteria. The patients selected from the CTEPH cohort are shown in figure 1. The control cohort comprised 51 patients with dyspnea and various underlying diseases. In the controls, CTEPH and PH had been excluded by imaging studies and right heart catheterization.

For the analysis of CPET data, $P(A\text{-a})\text{O}_2$ and $P(c\text{-ET})\text{CO}_2$ were evaluated at maximum exercise. PETCO_2 , EQO_2 and EQCO_2 were studied at AT. Additionally, the VE/VCO_2 slope was analyzed from the beginning up to respiratory compensation. Means and standard deviations were calculated for all parameters in CTEPH patients and controls. Statistical significance was expressed as p values with the t test and assumed if $p < 0.05$.

We performed receiver-operating curves (ROC) and calculated the Youden index to determine the optimal cutoff and to assess sen-

Fig. 1. Patient selection for the retrospective analysis. In all patients, CTEPH had been suspected due to an intravascular mass detected by CT or ventilation/perfusion (VQ) scan mismatch. Patients with incomplete data were excluded. Only patients with

complete data and mPAP ≥ 25 mm Hg at rest or, if mPAP at rest was < 25 mm Hg, mPAP at exercise > 30 mm Hg were included in the final analysis. Echo = Echocardiography; RHC = right heart catheterization; CPX = cycle ergometry.

Table 1. Anthropometric data of the patients with CTEPH and controls (means $\pm$ SD)

	CTEPH (n = 42)	Controls (n = 51)	p value
Males/females	14/28	10/41	
Age, years	64 $\pm$ 15	62 $\pm$ 14	0.44
Weight, kg	78 $\pm$ 13	78 $\pm$ 21	0.97
Height, cm	170 $\pm$ 7	167 $\pm$ 8	0.09
Body mass index	27.2 $\pm$ 4.7	27.9 $\pm$ 6.4	0.58
RVSP echo, mm Hg	67 $\pm$ 24	30 $\pm$ 4.5	< 0.001
mPAP, mm Hg	37 $\pm$ 15	15 $\pm$ 3	< 0.001
Pulmonary artery wedge pressure, mm Hg	10.6 $\pm$ 5	7 $\pm$ 4	< 0.001
Cardiac output, l/min	4.8 $\pm$ 1.1	5.1 $\pm$ 1.3	0.14
Cardiac index, l/min/m ²	2.6 $\pm$ 0.6	2.8 $\pm$ 0.7	0.25

sitivity and specificity of each parameter. Additionally, we developed two scores of the parameters: (a) VE/VCO₂ slope, PETCO₂, P(A-a)O₂ and P(c-ET)CO₂, and (b) EQO₂, EQCO₂, VE/VCO₂ slope, PETCO₂, P(A-a)O₂ and P(c-ET)CO₂. In order to establish these scores combining multiple CPET parameters, we performed a multivariate dis-

criminant analysis and determined coefficients for multiplying these with the measured values of the CPET parameters. The cutoff of the score value was determined by the mean of the group centroids of the CTEPH and control groups. To evaluate the quality of the scores and determine sensitivity and specificity, a leave-one-out cross-validation of the discriminant analysis was performed. Statistical analysis was performed using SSPS® (IBM, version 21.0).

Finally, all patients with proven CTEPH but normal echocardiographic findings were analyzed [right ventricular systolic pressure (RVSP) < 35 mm Hg or not detectable due to the absence of tricuspid valve insufficiency]. The study was approved by our local ethics committee and was in accordance with the current version of the Declaration of Helsinki. All patients gave written informed consent.

Results

Table 1 shows the anthropometric and hemodynamic data of with CTEPH patients and controls. Height, weight and age did not differ significantly. The control group consisted of patients with dyspnea; PH was excluded invasively (n = 51). These patients had the following underly-

Fig. 2. Parameters of CPET in CTEPH (n = 42) and control group (n = 51). * p < 0.001.

Table 2. Cutoff values, sensitivity and specificity of CPET data

Parameters	Cutoff	Sensitivity, %	Specificity, %
1 EQO_2	30.5	73.8	76.5
2 $EQCO_2$	35.5	73.8	76.5
3 VE/VCO_2	37.5	78.6	82.4
4 $PETCO_2$ at AT, mm Hg	31.33	78.6	82.4
5 $P(A-a)O_2$, mm Hg	36.97	78.6	88.4
6 $P(c-ET)CO_2$, mm Hg	5.18	85.7	88.2
7 Score calculated by 1-6	0.1052	81.0 ^a	92.2 ^a
8 Score calculated by 3-6	0.1048	83.3 ^a	92.2 ^a

^a Scores after cross-validation.

ing diseases: asthma (n = 7/13.7%), chronic obstructive pulmonary disease (n = 10/19.6%), interstitial lung disease (n = 3/5.9%), sleep apnea (n = 8/15.7%), coronary artery disease (n = 3/5.9%), chronic left ventricular insufficiency (n = 2/3.9%), diabetes (n = 9/17.6%), chronic renal disease (n = 5/9.8) and chronic thyroid disorder (n = 17/33.3%).

Each of the 6 CPET parameters evaluated differed significantly between CTEPH patients and controls (fig. 2).

We calculated two scores of the CPET parameters: (a) all 6 and (b) only 4 parameters: $P(A-a)O_2$, $P(c-ET)CO_2$, $PETCO_2$ and VE/VCO_2 slope. The score equation for the 6-parameter CPET (6-P-CPET) score is:

$$X = \text{score value} = [VE/VCO_2] * 0.033 + [EQO_2] * 0.004 + [EQCO_2] * (-0.020) + [PETCO_2] * (-0.027) + [P(A-a)O_2] * 0.043 + [P(c-ET)CO_2] * 0.087 + (-1.620), \text{ with a cutoff at } 0.1052 \text{ (value } \geq \text{ cutoff = abnormal).}$$

The score equation for the 4-parameter CPET (4-P-CPET) score is:

$$X = \text{score value} = [VE/VCO_2] * 0.025 + [PETCO_2] * (-0.021) + [P(A-a)O_2] * 0.044 + [P(c-ET)CO_2] * 0.084 + (-2.129), \text{ with a cutoff at } 0.1048 \text{ (value } \geq \text{ cutoff = abnormal).}$$

Table 2 provides the calculated cutoff values, and sensitivity and specificity of each single parameter and of the scores showing the highest sensitivity for $P(c-ET)CO_2$ (85.7%) and a specificity of 88.2%. Using the 4-P-CPET score leads to an improved specificity of 92.2% with a sensitivity of 83.3% after cross-validation. Figure 3 shows the ROC curves for the two scores.

RVSP was detectable and >35 mm Hg and echocardiography was able to identify PH in 29 of 42 patients

Fig. 3. ROC curves of the 4- (a) and the 6-P-CPET score (b).

with proven CTEPH (69%). In 13 patients with RVSP <35 mm Hg or unmeasurable RVSP due to the absence of tricuspid valve insufficiency, echocardiography was not able to detect PH (31%). In these patients, right heart catheterization revealed an mPAP of 30 ± 8 mm Hg at rest (range 19–47 mm Hg). Three of these patients showed an mPAP <25 mm Hg at rest, which increased to 38, 44 and 60 mm Hg during exercise.

We found an increased [15] right ventricular diameter in 15 of 42 CTEPH patients. The right atrial area was abnormal in 23 of 42 patients; 17 of the CTEPH patients had normal diameters of the right heart chambers. Finally, 6 of 13 patients with normal or undetectable RVSP showed abnormal right atrium and/or ventricle values. Seven patients showed neither pathological RVSP nor an abnormality in right heart chamber diameters, and in these patients PH was not detected by echocardiography. In these patients, mPAP was 30 ± 5 mm Hg.

All patients with normal or undetectable RVSP had an abnormal CPET. $P(c-ET)CO_2$ was >5.18 mm Hg in all patients with CTEPH (table 3). Twelve of the 13 patients with normal or undetectable RVSP were identified by both calculated CPET scores.

Four patients showed 6 pathological parameters, 6 had 5 pathological parameters, 2 had 4 parameters above the cutoff and 2 patients were at least positive for 2 CPET parameters (see online suppl. table; for all online suppl. material, see www.karger.com/doi/10.1159/000358565).

All 6 patients of the CTEPH cohort with normal resting hemodynamics but an increased mPAP during exer-

Table 3. Patients with pathological values (above cutoff) of CPET parameters and normal echocardiography (n = 13)

Parameters	Cutoff	'Positive', n
EQO ₂	(>30.5)	10 (77%)
EQCO ₂	(>35.5)	12 (92%)
VE/VCO ₂	(>37.5)	9 (69%)
P(A-a)O ₂ , mm Hg	(>36.97)	10 (77%)
P(c-ET)CO ₂ , mm Hg	(>5.18)	13 (100%)
PETCO ₂ , mm Hg	(<31.33)	10 (77%)
4-P-CPET score	(>0.1048)	12 (92%)
6-P-CPET score	(>0.1052)	12 (92%)

cise >30 mm Hg were detected by CPET. They showed at least 4 pathological CPET parameters. The mean of all tested CPET parameters of these patients was statistically significantly different from the mean of the parameters in the control cohort: EQO₂ (p = 0.001), EQCO₂ (p < 0.001), PETCO₂ (p < 0.001), VE/VCO₂ (p < 0.001), P(c-ET)CO₂ (p < 0.001) and P(A-a)O₂ (p = 0.002).

Discussion

Our study shows that CPET is a useful tool to detect CTEPH, even in patients in whom echocardiographic assessment showed normal RVSP or when RVSP was not detectable due to the absence of tricuspid valve insufficiency.

Despite improved survival due to modern management of CTEPH, including pulmonary endarterectomy [11, 27] and use of targeted therapies for nonoperable patients [27], CTEPH remains a serious and often life-threatening disease [27]. Survival might be affected by delayed diagnosis. Prognosis worsens with increasing WHO functional class [11] and outcome is generally poor in untreated patients [28, 29], which provides a strong rationale for the early detection of CTEPH. The use of a ventilation-perfusion scan and computed tomography as a primary tool to evaluate CTEPH in patients with exertional dyspnea and a history of acute PE is limited. The dynamic process of ongoing thrombus resolution and remodeling results in a poor correlation between vascular obstruction seen in these imaging modalities and PH [30, 31]. Additionally, the concern of radiation exposure limits the value of ventilation-perfusion scans as the first step in the diagnostic process.

Current guidelines recommend transthoracic echocardiography as the first noninvasive diagnostic tool in patients with suspected PH [12, 13]. However, echocardiography has limited sensitivity in early/mild PH. In our study, measurement of RVSP was only able to detect 29 (69%) of 42 patients with CTEPH. Echocardiography was performed by two highly experienced physicians, which makes it unlikely that the result was due to the lack of diagnostic skills and workup, but highlights the limitation of echocardiography in detecting early and mild PH. The findings are in line with reported sensitivity and specificity values in patients with PH and comorbid conditions [20]. Guidelines state clearly that indirect evidence of PH on echocardiography should trigger further investigation in the presence of a risk factor or symptoms [12, 14]. In our study, measurement of right ventricular diameter and right atrial area did improve the accuracy of detecting CTEPH, but 7 of 42 patients (16%) escaped echocardiographic detection. Furthermore, echocardiographic assessment of right heart chambers is limited by poor validation of the reference values. The guidelines recommend a cutoff value of 42 mm for basal right ventricular diameter and 18 cm² for right atrial area, but these values depend on age and gender. Lang et al. [32] only recommended measurement of right atrial minor axis. Grünig et al. [33] proposed to use gender-specific and even lower cutoff values. However, this meta-analysis was limited by the fact that the studies analyzed included primarily younger patients. The mean age in these studies was 22–45 years. The oldest single patient in this meta-analysis was 54 years old [33]. Additionally, right atrial area and right ventricular dimensions are affected by training status [33].

Patients with CTEPH typically present with exertional dyspnea but do not show severely disturbed resting hemodynamics at early stages. Therefore, we postulate that evaluating patients with exertional dyspnea and suspected PH or CTEPH by exercise testing might facilitate earlier detection of abnormalities compared to echocardiography at rest. Stress echocardiography, and strain and strain rate imaging might help to detect PH at early stages [34, 35], but these methods are yet to be validated [13, 35, 36]. In our study, we evaluated 36 patients with resting PH and 6 patients with an exercise-induced increase in mPAP but normal PAP at rest. All patients with exercise-induced PH and all patients with pathological PAP at rest showed abnormal patterns in CPET. Most patients showed 5 or 6 abnormal values out of the 6 test parameters. Although exercise-induced PH does not match the Dana Point definition of CTEPH, in daily practice, patients with previous PE and persistent dyspnea, endovascular abnormalities but normal resting hemodynamics are seen. Our data show that despite normal resting hemodynamics, these patients have abnormal CPET parameters, which are significantly different from the control cohort. These findings underscore that these patients seem to have functional limitations. Additionally, 4 of 6 patients with normal resting hemodynamics were technically operable. The 3 patients who underwent pulmonary endarterectomy improved significantly (data not shown).

Our data suggest that CPET might be a more sensitive tool than echocardiography and close the diagnostic gap between expected [4, 37] and actually known prevalence rates of CTEPH and therefore facilitate earlier diagnosis.

The potential value of CPET for CTEPH diagnosis has previously been demonstrated by Scheidl et al. [21]. However, in their study, CPET was evaluated to discriminate between CTEPH and PAH. The authors discussed whether the method would be also suitable to detect CTEPH in a less selected patient population. Our study has the advantage that it included a much higher number of CTEPH patients and did not compare patients with CTEPH with healthy individuals. Our control cohort included patients who presented with exertional dyspnea in whom CTEPH and PH had been excluded by right heart catheterization. Anthropometric data did not differ in both groups. The control group showed normal mPAP and a slightly decreased but nonsignificantly different cardiac index. When comparing CPET parameters in the CTEPH cohort with the non-healthy control group, we found a high sensitivity for the detection of CTEPH. Using a score combining 4 parameters, we found a higher specificity

than Scheidl et al. [21]. Hence, this underscores the value of CPET in detecting CTEPH.

Using the evaluated CPET parameters, the sensitivity and specificity for detecting PAH were lower than those for CTEPH (data not shown). This underscores the value of CPET to discriminate between these entities as it was already focused and clearly shown by Scheidl et al. [21]. Our study is not only confirming but also extends the results of Scheidl et al. [21], who originally identified the role of $P(c-ET)CO_2$ for the detection of CTEPH by reflecting disturbed perfusion and perfusion/ventilation imbalance. Our study included a much higher number of patients with CTEPH and we systematically evaluated 6 CPET parameters, which allowed us to establish a score of a combination of different variables. The determined cutoff for $P(c-ET)CO_2$ was slightly different from that published by Scheidl et al. [21], but sensitivity and specificity were comparable. $P(c-ET)CO_2$ seems to provide higher sensitivity than other single variables. $P(c-ET)CO_2$ showed nearly the same specificity as reported before.

VO_2 and $EQCO_2$ can be abnormal in PH [38] and decreased VO_2 has prognostic value [39]. In our study, both $EQCO_2$ and EQO_2 were significantly higher in patients with CTEPH compared to controls, although sensitivity and specificity were lower than other individual parameters. Scheidl et al. [21] reported a stronger correlation of $EQCO_2$ and VO_2 in patients with idiopathic PAH compared to CTEPH and explained this with the heterogeneity of pulmonary blood flow in CTEPH. During exercise, reduced and decreasing $PETCO_2$ levels have been reported for idiopathic PAH [40]. Dumitrescu et al. [22] found VE/VCO_2 at AT, $PETCO_2$ at AT and decreasing $PETCO_2$ from the start of exercise to AT to distinguish patients with pulmonary vasculopathy from those with normal pulmonary hemodynamics in scleroderma [22]. Our CTEPH cohort showed significantly different values for $PETCO_2$ at AT and VE/VCO_2 at AT compared to the control group.

However, sensitivity and specificity of $PETCO_2$ and VE/VCO_2 at AT did not reach the same level as $P(c-ET)CO_2$ and the established CPET score combining 4 parameters. $P(A-a)O_2$ showed a comparable sensitivity and higher specificity as $PETCO_2$ at AT and VE/VCO_2 , but sensitivity was lower than by using the 4-P-CPET score.

Combining individual parameters to the 4-P-CPET score increased specificity to >92% without substantially affecting sensitivity. Use of the score detected 12 of 13 patients with normal echocardiographic findings. $P(c-ET)CO_2$ was able to identify all patients with normal or undetectable RVSP.

Our study has several limitations, including its retrospective design, the relatively small number of patients and the fact that all data originate from a single, albeit specialized PH center. Since only patients with definite CTEPH were included, the present findings are not transferable to other PH forms, but this was not the purpose of the present investigation. Despite these limitations, the robustness of the data allow to postulate that CPET is able to detect CTEPH in patients with normal echocardiographic findings and may serve as a noninvasive diagnostic tool to rise the suspicion for CTEPH in patients with exertional dyspnea.

Conclusion

CPET is valuable as a complementary diagnostic tool for the detection of CTEPH in patients with suspected PH but normal echocardiography. All individual CPET parameters can help to distinguish between CTEPH and controls. However, the 4-P-CPET score provides the highest specificity and a high sensitivity. These findings should be confirmed in a prospective clinical trial.

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