

Featured Article

Enhanced external counterpulsation on exercise tolerance in pneumoconiosis: Insights from comorbidity subgroups efficacy and predictors

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Abstract: Background: To investigate the efficacy of enhanced external counterpulsation (EECP) in improving exercise tolerance in patients with pneumoconiosis, focusing on differences in efficacy with and without lung disease comorbidities, and to identify key predictors of EECP efficacy. **Patients and methods:** Seventy patients with occupational pneumoconiosis were enrolled in a single-center randomized controlled trial, and were randomly divided into the conventional group (35 patients) and the EECP group (35 patients), and according to the presence or absence of lung disease comorbidities, subjects were divided into the subgroups with and without comorbidities. The conventional group received health management, medication, and individualized exercise prescription, while the EECP group received 1 h of EECP intervention per day for 5 weeks on top of the conventional treatment. Exercise tolerance indexes before and after treatment were assessed by cardiopulmonary exercise test (CPET), including AT-VO₂Kg, Max-VO₂Kg, AT-O₂puls, Max-O₂puls, AT-Load, AT-Mets and Max-Mets 7 indicators. Predictors of efficacy were analyzed by univariate and multivariate linear regression using post-treatment AT-VO₂Kg as the main dependent variable. **Results:** Comparison of all CPETs between the EECP and non-EECP groups, and the comorbidity subgroup and the uncomplicated subgroup before treatment showed no statistically significant difference ($P > 0.05$), and the post-treatment AT-VO₂Kg, Max-VO₂Kg, AT-O₂puls, Max-O₂puls, and metabolic equivalents of the EECP group and the uncomplicated subgroup (AT-Mets, Max-Mets) were significantly improved compared with the control group (all $P < 0.05$), but no significant benefit was seen in the comorbidity subgroup ($P > 0.05$). Multiple regression analysis showed that comorbidity was a negative predictor of efficacy whereas pre-treatment AT-VO₂Kg was a positive predictor. No safety adverse events occurred in either group. **Conclusion:** EECP safely and effectively improved exercise tolerance in patients with pneumoconiosis, and its efficacy was particularly significant in the comorbidity-free subgroup. The comorbidity subgroup failed to benefit significantly from the EECP intervention, and further analysis showed that comorbidity was an independent negative predictor limiting the treatment effect. In addition, pretreatment AT-VO₂Kg served as a positive predictor of efficacy, suggesting that patients with higher baseline cardiorespiratory reserve had a superior benefit from EECP treatment.

Keywords: pneumoconiosis; comorbidities; enhanced extracorporeal counterpulsation (EECP); exercise endurance; cardiorespiratory fitness

1. Introduction

Pneumoconiosis is an irreversible respiratory disease caused by long-term occupational dust exposure with pulmonary fibrosis as the core pathological feature, which leads to progressive decline in lung function, impaired exercise tolerance and deterioration in quality of life. Epidemiologic data show that the incidence of comorbidities (such as chronic obstructive pulmonary disease, pulmonary heart disease, and metabolic syndrome) is as high as 48.5%, and that comorbidities are the main cause of exacerbation and death in patients with pneumoconiosis [1]. Current therapeutic strategies can partially relieve symptoms, but it is difficult to reverse the pathological process, and patients are often repeatedly hospitalized due to cardiorespiratory decompensation. Globally, pneumoconiosis remains an important public health problem. Although the incidence of pneumoconiosis has declined in some countries through enhanced occupational protective measures and improved working environments, the burden of pneumoconiosis remains heavy in developing countries [2,3]. In recent years, exercise tolerance has attracted much attention as a key indicator for assessing cardiopulmonary reserve function and predicting all-cause mortality [4], and patients with pneumoconiosis generally have low exercise tolerance due to dysregulated ventilation/blood flow ratio and diffusion dysfunction. Pneumoconiosis is incurable, and most pharmacological treatments can only delay pulmonary fibrosis and reduce symptoms, which highlights the urgency of novel therapeutic modalities [5].

Enhanced External Counterpulsation (EECP) is a noninvasive assisted circulation technique that improves hemodynamics through sequential pressurization of the lower extremities, and its mechanism of action involves diastolic pressurization waves to increase coronary perfusion, reduce cardiac afterload, and promote neovascularization, etc. [6,7], which has been shown to have clear efficacy in cardiovascular disease rehabilitation. shown clear efficacy. Recent studies have further revealed that EECP can improve cardiopulmonary function and increase exercise tolerance in patients with chronic coronary artery disease (CAD) [8], and some studies have also shown that EECP can improve exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) [9]. The results of the available studies provide theoretical support for EECP in improving cardiorespiratory fitness and enhancing exercise endurance; however, the evidence for the efficacy of EECP in pneumoconiosis, a group characterized by pulmonary fibrosis, is still extremely limited, and the heterogeneity of comorbidities on the therapeutic response has not been systematically assessed. The present study is based on an extended analysis of the same cohort, and the preliminary results suggest that extracorporeal counterpulsation significantly enhances $AT-VO_2/kg$, $Max-VO_2Kg$, and $Max-O_2puls$ in patients with pneumoconiosis, and the related results are being published. To further explore the efficacy heterogeneity and individualized prediction model of EECP, the present study was upgraded to a multidimensional analysis framework by adding dynamic indicators such as $AT-Mets$, $Max-Mets$, $AT-Load$, and $AT-O_2puls$, and for the first time, the difference in efficacy was assessed by stratifying by comorbidity subgroups and uncomplicated subgroups. Meanwhile, the relationship between BMI, age, blood gas analysis, hsCRP, lung function and EECP efficacy was

analyzed by multivariate regression modeling, aiming to construct an individualized efficacy prediction system based on clinical characteristics, and to provide precise intervention targets for multidisciplinary rehabilitation of pneumoconiosis.

2. Materials and methods

2.1. Subjects

Patients diagnosed with occupational pneumoconiosis and treated at Guangxi Workers' Hospital from January 2023 to December 2024, who volunteered to participate in this study, were selected as study subjects. Inclusion criteria: (1) age $\geq$ 18 years old, gender is not limited; (2) diagnosis of occupational pneumoconiosis; (3) signed informed consent and the protocol was certified by the hospital ethics committee. Subjects were excluded from the study if they suffered from severe cardiac, pulmonary, hepatic, renal or other systemic diseases and those with contraindications to EECP (thrombosis, hemorrhagic disorders, encephalopathy, uncontrolled hypertension, uncontrolled cardiac arrhythmia, acute heart failure, lower limb arterial stenting, and pregnancy, etc.).

2.2. General information collection

General data of patients were collected, including gender, age, smoking history, body mass index (BMI), blood pressure, blood gas analysis (PaO₂, OI), left ventricular ejection fraction (LVEF%), pulmonary function (FVC, FEV₁, FEV₁/FVC), and comorbidities of lung diseases.

2.3. Randomization, subgroups and interventions

A total of 70 patients met the inclusion criteria and completed the study. Subjects were divided into EECP and non-EECP groups in a 1:1 ratio according to a voluntary and randomization scale, and into subgroups with and without comorbidities according to the presence or absence of comorbidities of other lung diseases.

Non-EECP group: health management according to the clinical diagnosis and treatment guideline, advising patients to quit smoking, detach from dusty working life, strengthen nutrition, enhance physical exercise, aerobic exercise (brisk walking, power car) as the main health management; according to the clinical symptoms, anti-fibrosis, cough, phlegm, asthma medication; according to the presence or absence of complications to provide symptomatic treatment. EECP group: the above conventional treatment + EECP (Omaxe), pressure 0.03–0.045 kPa, operated by an experienced and trained doctor. EECP group: the above conventional treatment + EECP (OM-A balloon external counterpulsation system), pressure 0.03–0.045 kPa, an experienced and well-trained doctor operated the equipment. all subjects in the EECP group were treated with EECP for 1 h per day for 5 weeks for a total of 35 sessions, and evaluated at week 6.

2.4. Assessment of indicators

Cardiopulmonary Exercise Test (CEPT): The Swiss Schiller 104T

cardiopulmonary function tester was used to perform CPET on a bicycle one day before EECPT treatment and the day after the end of EECPT treatment. Tests for the two groups of patients before and after treatment included anaerobic threshold oxygen uptake (AT-VO₂Kg), maximal oxygen uptake (Max-VO₂Kg), anaerobic threshold pulses (AT-O₂puls), maximal oxygen threshold pulses (Max-O₂puls), anaerobic threshold training load (AT-Load), anaerobic threshold metabolic equivalents (AT-Mets) and maximal metabolic equivalents (Max-Mets).

2.5. Linear regression analysis

AT-VO₂Kg is a key indicator of CEPT, reflecting the efficiency of patients' oxygen uptake at daily activity levels. In this study, in order to investigate the influencing factors of exercise endurance after EECPT treatment, a linear regression analysis was performed using post-treatment AT-VO₂Kg as the dependent variable, and a univariate analysis was performed using the collected general information of the patients as well as the baseline AT-VO₂Kg prior to the treatment as the independent variable, and a statistically significant independent variable was included in the multifactor linear regression model. Statistically significant independent variables were included in the multifactorial linear regression model to further control for potential confounders and clarify the independent effects of each factor on AT-VO₂Kg.

2.6. Statistical methods

Statistical analyses were performed using SPSS 27.0, and for numerical variables, normality tests were first performed; if normality was satisfied in all groups, $\bar{x} \pm s$ was used to indicate the normality, and independent samples *t*-tests were used for between-group comparisons; otherwise, the median (interquartile spacing) was used to describe the statistic, and Mann-Whitney *U*-tests were used for between-group comparisons. Categorical variables were expressed as frequencies (percentages) and compared using the chi-square test or Fisher's exact test. Multifactorial analyses were performed using linear regression analysis, and regression results were visualized using GraphPad Prism 10. All tests were two-sided, and the effects analyzed were pre- and post-treatment differences and corresponding *p*-values and 95% CIs, with a *p*-value < 0.05 considered statistically significant.

2.7. Safety assessment

This study closely monitors the vital signs of the subjects (including heart rate, blood pressure, etc.), and systematically records adverse events related to treatment, such as limb numbness, chest pain, etc. At the same time, continuous ECG monitoring is used to ensure the early identification and intervention of cardiovascular adverse events such as malignant arrhythmias. Provides comprehensive data for the safety of the study.

3. Results

3.1. Comparison of general information

The two groups were compared in terms of gender, age, blood pressure, body mass index (BMI), smoking prevalence, oxygenation index, left ventricular ejection fraction (LVEF%), pulmonary function, and comorbidities (co-tuberculosis, infections, COPD, and bronchiectasis, etc.), and the differences were not statistically significant ($P > 0.05$) (Table 1).

Table 1. Comparison of general information.

	Non-EECP group (<i>n</i> = 35)	EECP group (<i>n</i> = 35)	<i>P</i>
Male	35	35	
Age	51 (48, 57)	55 (47, 60)	0.522
Smoking (%)	16 (45.7%)	19 (54.3%)	0.473
BMI (Kg/m ²)	24.17 ± 3.26	23.19 ± 2.42	0.162
SBP (mmHg)	128.86 ± 13.12	131.00 ± 12.40	0.485
DBP (mmHg)	82.77 ± 8.25	83.09 ± 8.30	0.874
OI (mmHg)	409.80 ± 53.24	418.11 ± 98.80	0.663
hsCRP (mg/L)	1.10 (0.60, 1.90)	0.90 (0.50, 2.30)	0.864
LVEF (%)	67.63 ± 6.35	68.34 ± 4.93	0.601
FEV1/FVC (%)	77.83 (72.10, 80.46)	75.95 (68.34, 79.73)	0.299
Complications (%)	16 (45.7%)	17 (48.6%)	0.811

3.2. Comparison of exercise endurance

Comparing the two groups before and after treatment, the differences in AT-VO₂Kg, Max-VO₂Kg, AT-O₂puls, Max-O₂puls, AT-Load, AT-Mets, and Max-Mets between the EECP group and the non-EECP group were not statistically significant before treatment ($P > 0.05$), and after treatment, except for AT-Load ($P > 0.05$), the remaining indicators the EECP group showed significant improvement compared with the non-EECP group ($P < 0.05$) (Table 2).

Table 2. Comparison of exercise endurance between EECP and non-EECP groups.

Parameter	Non-EECP groups (<i>n</i> = 35)			EECP groups (<i>n</i> = 35)			<i>P</i>	95%CI
	Before	After	Δvalue (After-Before)	Before	After	Δvalue (After-Before)		
AT-VO ₂ Kg	13.79 ± 2.30	14.93 ± 2.36	1.14 ± 1.89	14.09 ± 2.28	16.05 ± 2.21	1.96 ± 2.50	0.044	−2.21, −0.03
Max-VO ₂ Kg	20.63 ± 4.18	22.66 ± 3.79	2.03 ± 1.90	20.65 ± 4.26	24.58 ± 3.78	3.93 ± 4.30	0.038	−3.72, −0.11
AT-O ₂ puls	8.42 ± 1.16	8.73 ± 1.30	0.30 ± 1.23	8.48 ± 1.22	9.39 ± 1.46	0.91 ± 1.27	0.048	−1.32, −0.01
Max-O ₂ puls	10.43 ± 1.62	10.72 ± 1.49	0.29 ± 1.01	10.23 ± 1.49	11.85 ± 1.89	1.62 ± 1.46	0.007	−1.94, −0.31
AT-Load	59 (52, 65)	62 (55, 69)	2.91 ± 7.70	62 (54, 79)	68 (58, 81)	5.31 ± 13.95	0.059	−11.24, 0.44
AT-Mets	3.95 ± 0.66	4.26 ± 0.68	0.32 ± 0.54	4.03 ± 0.65	4.61 ± 0.63	0.59 ± 0.74	0.028	−0.66, −0.04
Max-Mets	5.90 ± 1.20	6.50 ± 1.08	0.57 ± 0.54	5.91 ± 1.21	7.00 ± 1.11	1.09 ± 1.25	0.045	−1.06, −0.01

3.3. Subgroup analysis

3.3.1. Non-comorbidities subgroup

The two groups (EECP group, *n* = 18; non-EECP group, *n* = 19) showed no statistically significant differences in general data, AT-VO₂Kg, Max-VO₂Kg, AT-O₂,

AT-O₂puls, and Max-Mets before treatment ($P > 0.05$); after treatment comparison, all CPET indicators in the EECp group improved significantly compared to the non-EECP group ($P < 0.05$ for all) (Tables 3 and 4).

Table 3. Comparison of general information in the non-comorbidities subgroup.

	Non-EECP group (<i>n</i> =19)	EECP group (<i>n</i> =18)	<i>P</i>
Age	51.00 (48.00, 54.00)	53.00 (43.75, 56.00)	0.879
Smoking (%)	11 (57.9%)	11 (61.1%)	0.842
BMI (Kg/m ²)	23.59 ± 2.71	23.29 ± 1.95	0.698
SBP (mmHg)	127.53 ± 11.61	127.56 ± 10.2	0.994
DBP (mmHg)	82.11 ± 7.77	83.00 ± 7.89	0.730
OI (mmHg)	424.00 (376.00, 452.00)	452.50 (409.75, 520.25)	0.114
hsCRP (mg/L)	1.20 (0.70, 1.70)	0.85 (0.50, 2.125)	0.572
LVEF (%)	68.00 (65.00, 71.00)	70.50 (67.50, 73.00)	0.179
FEV1/FVC (%)	80.01 (70.74, 80.39)	79.30 (73.39, 82.83)	0.879

Table 4. Comparison of exercise endurance in the non-comorbidities subgroup.

Parameter	Non-EECP groups (<i>n</i> = 19)		Δvalue (After-Before)	EECP groups (<i>n</i> = 18)		Δvalue (After-Before)	<i>P</i>	95%CI
	Before	After		Before	After			
AT-VO ₂ Kg	14.01 ± 2.31	15.38 ± 2.45	1.37 ± 1.76	14.15 ± 1.98	17.11 ± 2.39	2.96 ± 2.28	0.037	−3.34, −0.11
Max-VO ₂ Kg	21.34 ± 4.77	23.29 ± 3.77	1.95 ± 1.95	21.06 ± 5.0	26.4 ± 3.22	5.34 ± 4.03	0.011	−5.46, −0.77
AT-O ₂ puls	8.21 ± 1.07	8.389 ± 1.36	0.17 ± 1.02	8.76 ± 1.22	9.98 ± 1.30	1.23 ± 0.76	< 0.001	−2.48, −0.71
Max-O ₂ puls	10.35 ± 1.57	10.46 ± 1.22	0.12 ± 0.97	10.69 ± 1.79	12.59 ± 1.60	1.9 ± 1.03	< 0.001	−3.07, −1.18
AT-Load	58.68 ± 10.22	59.00 (54.00, 69.00)	4.37 ± 6.95	63.44 ± 14.94	78.50 (66.00, 83.00)	11.0 ± 13.17	0.009	−18.90, −3.88
AT-Mets	4.02 ± 0.67	4.40 ± 0.70	0.38 ± 0.50	4.04 ± 0.68	4.88 ± 0.68	0.84 ± 0.65	0.038	−0.95, −0.03
Max-Mets	6.11 ± 1.36	6.65 ± 1.08	0.54 ± 0.54	6.02 ± 1.41	7.53 ± 0.93	1.51 ± 1.14	0.011	−1.56, −0.21

3.3.2. Comorbidity subgroup

The differences in general information, AT-VO₂Kg, Max-VO₂Kg, AT-O₂, AT-O₂puls, and Max-Mets between the two groups (EECP group, $n = 16$; non-EECP group, $n = 17$) before treatment were not statistically significant ($P > 0.05$); in comparison of the two groups after treatment, the improvement of all CPET indicators in the EECp group was not significant compared with that in the non-EECP group (P all > 0.05) (Tables 5 and 6).

Table 5. Comparison of general information in the comorbidities subgroup.

	Non-EECP group (<i>n</i> = 16)	EECP group (<i>n</i> = 17)	<i>P</i>
Age	53.31 ± 7.03	57.12 ± 11.35	0.259
Smoking (%)	5 (31.3%)	8 (47.1%)	0.353
BMI (Kg/m ²)	24.85 ± 3.8	23.1 ± 2.90	0.145
SBP (mmHg)	130.00 (117.25, 142.75)	140.00 (127.00, 145.00)	0.417

Table 5. (Continued).

	Non-EECP group (n = 16)	EECP group (n = 17)	P
DBP (mmHg)	80.50 (75.50, 92.75)	85.00 (78.50, 88.50)	0.986
OI (mmHg)	412.00 (375.75, 432.00)	395.00 (320.00, 424.00)	0.279
hsCRP (mg/L)	1.00 (0.50, 2.28)	1.00 (0.55, 3.30)	0.715
LVEF (%)	67.81 ± 7.96	67.47 ± 5.01	0.883
FEV1/FVC (%)	76.26 (72.46, 78.18)	73.23 (64.15, 76.20)	0.066

Table 6. Comparison of exercise endurance in the comorbidities subgroup.

Parameter	Non-EECP groups (n = 16)		Value (After-Before)	EECP groups (n = 17)		Value (After-Before)	P	95%CI
	Before	After		Before	After			
AT-VO ₂ Kg	13.52 ± 2.34	14.38 ± 2.19	0.86 ± 2.07	14.02 ± 2.62	14.92 ± 1.32	0.91 ± 2.35	0.393	-1.82, 0.73
Max-VO ₂ Kg	19.78 ± 3.32	22.20 (20.45, 25.25)	2.13 ± 1.90	20.22 ± 3.40	21.90 (20.40, 23.10)	2.43 ± 4.17	0.857	-3.29, 1.82
AT-O ₂ puls	8.20 (7.73,9.25)	9.13 ± 1.13	0.46 ± 1.47	8.20 (7.20, 9.15)	8.76 ± 1.38	0.56 ± 1.61	0.412	-0.53, 1.26
Max-O ₂ puls	10.54 ± 1.73	11.03 ± 1.74	0.49 ± 1.04	9.74 ± 1.40	11.07 ± 1.89	1.33 ± 1.81	0.958	-1.33, 1.26
AT-Load	62.31 ± 13.04	62.50 (55.00, 70.25)	1.19 ± 8.4	63.24 ± 18.09	66.00 (53.00, 68.50)	-0.71 ± 12.41	0.928	-7.60, 9.54
AT-Mets	3.86 ± 0.67	4.11 ± 0.64	0.24 ± 0.60	4.01 ± 0.76	4.33 ± 0.42	0.32 ± 0.76	0.243	-0.61, 0.16
Max-Mets	5.66 ± 0.96	6.35 (5.83, 7.18)	0.6 ± 0.55	5.79 ± 0.98	6.30 (5.85, 6.60)	0.65 ± 1.25	0.843	-0.93, 0.56

3.3.3. Multivariate predictors of post-treatment AT-VO₂Kg

A one-way regression analysis with general information and baseline AT-VO₂Kg as independent variables in the EECP group yielded PaO₂, AT-VO₂Kg (Before), and Complications as possible factors influencing the efficacy of the treatment, and a multiple linear regression analysis of these three factors was performed to determine the two independent predictors of AT-VO₂Kg after treatment (Table 7).

Key findings: comorbidities showed the strongest negative correlation with post-treatment AT-VO₂Kg ($P = 0.011$), and baseline levels of pre-treatment AT-VO₂Kg were positively correlated with treatment outcome (Figure 8).

Non-significant factors: age, smoking history, blood pressure, BMI, blood gases, hsCRP, pulmonary function and left ventricular ejection fraction were not statistically significant in the adjusted model ($P > 0.05$).

Table 7. Multivariate predictors of post-treatment AT-VO₂Kg.

Variables	Univariate analysis		Multivariate analysis	
	P	B (95%CI)	P	B (95%CI)
Age	0.237	-0.045 (-0.121, -0.031)	—	—
Smoking	0.700	-0.296 (-1.844, 1.252)	—	—
BMI	0.837	-0.006 (-0.070, 0.057)	—	—
SBP	0.981	0.001 (-0.093, 0.096)	—	—

Table 7. (Continued).

Variables	Univariate analysis		Multivariate analysis	
	<i>P</i>	<i>B</i> (95%CI)	<i>P</i>	<i>B</i> (95%CI)
BMI	0.158	−0.223 (−0.536, 0.091)	—	—
PaO ₂	0.011	0.061 (0.015, 0.107)	0.257	0.026 (−0.020, 0.072)
OI	0.105	0.006 (−0.001, 0.014)	—	—
hsCRP	0.293	−0.255 (−0.740, 0.230)	—	—
LVEF	0.089	0.131 (−0.021, 0.283)	—	—
FVC	0.094	0.913 (−0.165, 1.991)	—	—
FEV1	0.054	1.063 (−0.019, 2.145)	—	—
FEV1/FVC	0.233	0.054 (−0.036, 0.144)	—	—
AT-VO ₂ Kg (Before)	0.024	0.039 (0.051, 0.686)	0.025	0.322 (0.043, 0.601)
Complications	0.002	−2.018 (−3.522, −0.843)	0.011	−1.801 (−3.165, −0.436)

Statistically significant values are identified in boldface.

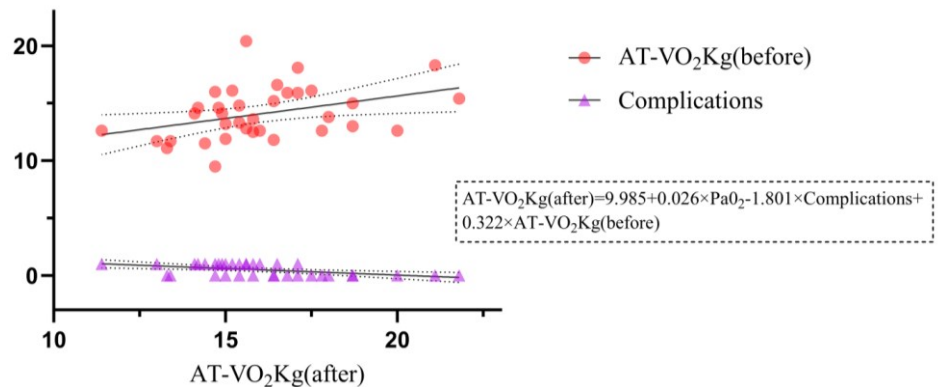


Figure 8. Visualization of regression analysis of factors influencing AT-VO₂Kg (after) in the EECp group.

3.3.4. safety

No subjects experienced any adverse events in this trial.

4. Discussion

As an objective quantitative method to assess cardiopulmonary reserve function and exercise capacity, CPET is valuable in the functional assessment of chronic respiratory diseases. pneumoconiosis, as an occupational pulmonary fibrosis disease, is often accompanied by progressive lung function impairment and reduced exercise tolerance in its pathological progression. In this study, we systematically evaluated the effect of enhanced external counterpulsation (EECP) on the improvement of exercise tolerance in patients with pneumoconiosis by means of a prospective cohort study design and revealed the heterogeneous characteristics of its efficacy. The results showed that EECP significantly improved exercise endurance indices (AT-VO₂Kg, Max-VO₂Kg, and metabolic equivalents) in the uncomplicated subgroup, however, no significant therapeutic benefit was observed in the comorbid lung disease subgroup. Multiple regression modeling further revealed that comorbidity status and baseline AT-VO₂kg level could serve as independent

predictors of EECp efficacy. This finding provides a new direction for non-pharmacological rehabilitation of pneumoconiosis, and suggests that patients' comorbidity status and cardiopulmonary reserve should be comprehensively assessed before EECp treatment in order to achieve accurate efficacy prediction.

Although the efficacy of extracorporeal counterpulsation (EECP) in cardiovascular diseases (e.g., coronary artery disease) as well as chronic obstructive pulmonary disease (COPD) has been widely validated, its application in the field of pneumoconiosis is still a gap. The results of the study showed that in terms of elevating maximal oxygen uptake (Max-VO_2) and anaerobic threshold (AT), the performance of pneumoconiosis patients treated with EECp was consistent with the results of previous studies [9,10]. However, pneumoconiosis and COPD are fundamentally different in terms of pathomechanisms, with pneumoconiosis characterized by pulmonary fibrosis at its core, whereas COPD manifests mainly as airway obstruction. Even so, the fact that EECp has demonstrated efficacy in these two very different diseases strongly suggests that EECp may act through common hemodynamic improvement and endothelial function regulation mechanisms. Potential mechanisms for its enhancement of exercise tolerance in patients with pneumoconiosis: (1) EECp mimics the effects of extracorporeal counterpulsation through the technique of periodic sequential pressurization, which can significantly increase venous return blood volume, increase per-beat output, and simultaneously improve blood flow distribution in the systemic vascular bed [11]. This optimized hemodynamic pattern enhances the efficiency of skeletal muscle oxygen supply under exercise load conditions, providing a key foundation for enhancing muscle aerobic metabolism and delaying the fatigue threshold. (2) Periodic hemodynamic shear stress activates endothelial-type nitric oxide synthase (eNOS), resulting in increased NO release. This molecule enhances the vascular smooth muscle diastolic response (decreasing peripheral resistance), inhibits platelet aggregation and inflammatory cell adhesion, and promotes the expression of vascular neovascularization-related factors (VEGF, bFGF). Notably, clinical studies have confirmed that shear stress treated with EECp also significantly reduces the levels of circulating inflammatory markers, including $\text{TNF-}\alpha$, MCP-1, sVCAM-1, hsCRP and 8-iso-PGF 2α [12], suggesting a clear anti-inflammatory and antioxidant effect. (3) EECp can improve glucose metabolism and enhance muscle metabolic activity. Relevant studies have shown that after EECp treatment in patients with type 2 diabetes mellitus, the insulin sensitivity of the patients was elevated, insulin resistance was improved, and at the same time, the expression of GLUT-4 protein was significantly increased after the treatment (the elevation was up to 47%) [13], a phenomenon that strongly suggests that the potential of skeletal muscle for glucose uptake has been dramatically improved. In addition, Michael Melin et al. found a significant increase in the expression of FG-2 and IGF-1 in skeletal muscle after EECp treatment [14], suggesting that mechanical stress stimulation most likely enhances the metabolic activity of the muscle by activating the growth factor pathway. This metabolic remodeling effect provides a material basis for exercise endurance enhancement. (4) Changes in arterial pressure triggered by EECp therapy may lead to vasodilation and stimulation of pressure receptors. The pressure reflex is a control mechanism based on the stimulation of sympathetic and vagal signaling

[15], and its activation results in a decrease in sympathetic activity and an increase in vagal tone, a neuromodulatory effect that significantly improves cardiovascular reactivity and prolongs exercise duration during exercise [16]. (5) In the respiratory system, its mechanism of action may lie in the fact that EECP effectively improves pulmonary blood flow conditions and optimizes the ventilation/blood flow ratio, which in turn indirectly enhances pulmonary oxygenation function [8,17].

Subgroup analyses showed that the efficacy of EECP was more conclusive in patients without comorbidities. This phenomenon may be due to the fact that patients without comorbidities have a relatively homogeneous process of pulmonary fibrosis, and EECP may be more likely to improve their ventilation/blood flow imbalance through the mechanisms described above. The discovery of comorbidities as negative predictors is clinically important. Comorbidities are due to synergistic interactions of pathologies or mechanisms, such as oxidative stress, inflammatory response, and immune imbalance pathways common to infections, COPD, tuberculosis, and dust, as well as their own specific mechanisms such as fibrotic mechanisms in pneumoconiosis, α 1-antitrypsin imbalance in COPD and branchial expansion, and interference of *Mycobacterium tuberculosis* with Th1 function through multiple virulence factors [5,18–20]. This multidimensional pathologic linkage ultimately leads to a significant increase in the difficulty of treatment thereby affecting the efficacy of EECP. The discovery of pre-treatment AT-VO₂Kg as a positive predictor suggests that patients with higher baseline cardiorespiratory reserve have a superior benefit of EECP therapy. However, this study has the following limitations: small sample size, limiting the analysis of subgroups of subdivided comorbidities (e.g., tuberculosis, pulmonary heart disease, COPD); short follow-up time, lack of long-term safety and efficacy data; insufficient mechanistic studies, did not detect the effect of EECP on lung fibrosis markers (e.g., TGF- β 1, collagen deposition), and needs to be further verified by animal experiments or molecular biology methods to test its anti fibrosis mechanism; few observation indexes, future research can integrate DLCO (carbon monoxide diffusion volume), NT-proBNP (N-terminal brain natriuretic peptide precursor), HRV (heart rate variability), 6-min walk test and other indexes to realize accurate rehabilitation evaluation; monotization of device parameters, the same pressure range of EECP was used in all patients (0.03~0.045 kPa), and the optimization of individualized therapeutic regimen was not explored. explore the optimization of individualized treatment plan.

Taken together, EECP can safely and effectively improve the exercise endurance of patients with pneumoconiosis, and its efficacy is particularly significant in the non-complicated subgroup. Multiple regression modeling revealed that comorbidities were an independent negative predictor limiting the therapeutic efficacy, whereas pre-treatment AT-VO₂Kg level served as a positive predictor, suggesting that patients with better baseline cardiorespiratory fitness would be more likely to benefit from the intervention of EECP. In the future, more patients with comorbidities can be included to verify the efficacy of EECP in complex cases; the molecular pathways of EECP in regulating pulmonary fibrosis can be further analyzed by combining with transcriptomics or proteomics; and the optimization of EECP parameters based on the pneumoconiosis stage and comorbidities can also be

explored, and so on. The results of this study not only provide a new basis for the clinical application of EECP, but also open up an innovative direction for mechanical stress intervention in pulmonary fibrosis, which is worthy of promotion.

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Abbreviations

EECP	enhanced external counterpulsation
CPET	cardiopulmonary exercise test
AT-VO ₂ Kg	anaerobic threshold
Max-VO ₂ Kg	maximal oxygen Uptake
AT-O ₂ puls	anaerobic threshold oxygen pulse
Max-O ₂ puls	maximal oxygen pulse
AT-Load	anaerobic threshold load
AT-Mets	anaerobic threshold metabolic equivalent of task
Max-Mets	maximal metabolic equivalent of task
CAD	coronary artery disease
COPD	chronic obstructive pulmonary disease

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