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Enhanced External Counterpulsation Improves Dyspnea, Fatigue, and Functional Capacity in Patients with Long COVID

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Abstract: Approximately 31% of patients previously infected with SARS-CoV-2 are living with symptoms of long COVID in the United States. Long COVID significantly reduces quality of life and increases morbidity and disability; however, treatment options are limited. Enhanced External Counterpulsation (EECP) is an FDA-approved, non-invasive treatment for the management of cardiovascular symptoms with a mechanism of action which stimulates pathways that induce endothelial homeostasis, improving microvascular function, inflammation, and immune regulation, thereby potentially targeting the underlying etiology of long COVID. We recently reported that EECP improved symptoms in 231 patients with long COVID. Previous studies assessing the effects of EECP for long COVID have lacked a control group. As such, this analysis is the first comparing outcomes in patients with long COVID undergoing EECP (n = 33) to a non-treated group (control, n = 33). The patients were matched for baseline characteristics, and all patients completed patient-reported outcome assessments, including PROMIS Fatigue, the Duke Activity Status Index (DASI), and the Rose Dyspnea Scale (RDS), two times within a specified time interval. When comparing the average change from baseline in both groups, the EECP-treated patients' improvement was significantly greater than the improvement in the control group across all measured endpoints, including PROMIS Fatigue (-15.0 ± 8.9 vs. -2.8 ± 5.9, $p < 0.001$) and DASI (+17.8 (11.8, 26.8) vs. +1.8 (-3.5, 5.5), $p < 0.001$), and there was an improvement of $\geq$1 in the RDS class (75.8% vs. 33.3%, $p < 0.001$). This study's limitations include the small sample size and lack of information regarding concurrent treatments or interventions in the non-treated group; however, these preliminary data support EECP as a potential low-risk treatment option for patients with long COVID.

Keywords: long COVID; PASC; enhanced external counterpulsation; EECP

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1. Introduction

Post-acute sequelae of COVID-19 (PASC), commonly referred to as long COVID, is estimated to affect 31% of patients who were previously infected with SARS-CoV-2 in the United States (US) [1]. Commonly reported symptoms of long COVID include fatigue, neurologic manifestations such as brain fog and concentration impairment, and pulmonary or cardiovascular sequelae [2]. Prevalent symptoms, such as chest pain, dyspnea, and fatigue, have a profound impact on quality of life, interpersonal relationships, and disability,

affecting the workforce [3]. Among adults who worked prior to contracting COVID-19, over 50% are out of work or working fewer hours due to long COVID [4]. The proven treatment options for long COVID are limited [5,6], with federal organizations urging countries to prioritize therapeutic and rehabilitative strategies for long COVID [7].

Enhanced External Counterpulsation (EECP) is a Food and Drug Administration (FDA)-approved, non-invasive, underutilized treatment for refractory angina and ischemic heart failure that is safe and highly effective for the management of cardiovascular symptoms, including chest pain, shortness of breath, and fatigue—symptoms with a high burden in patients with long COVID [8,9]. During EECP therapy, blood pressure-like cuffs inflate and deflate in time with the cardiac cycle, which increases diastolic blood flow to the heart and decreases afterload during systole. Treatment with EECP also provides an increase in pulsatile shear stress (PSS). These hemodynamic and peripheral mechanisms lead to improved endothelial function and reduced inflammation [10]. EECP was first shown to effectively manage long COVID symptoms and improve quality of life in a 38-year-old patient in 2020 [11]. We recently published a series of data on 231 patients with long COVID undergoing EECP, demonstrating significant improvements in fatigue, chest pain, dyspnea, exercise tolerance, and quality of life [12]. Benefits in long COVID-related brain fog/cognitive impairment have also been demonstrated post-EECP in a cohort of 38 patients with objectively defined cognitive impairment at baseline [13]. Additionally, in a cohort of patients with long COVID with diagnosed coronary microvascular dysfunction (CMD), Wu et al. recently demonstrated significant improvements in angina and fatigue after treatment with EECP [14].

A limitation of previous studies assessing the effects of EECP for long COVID is the lack of a control group [11–14]. Moreover, there are few or no available treatment options for long COVID that have been rigorously tested in clinical trials [6]. The objective of this analysis is to compare outcomes in patients with long COVID undergoing EECP to a non-treated population of patients with long COVID. Our hypothesis was that patients with long COVID treated with EECP would have improved symptoms compared to the matched controls.

2. Materials and Methods

2.1. Study Design

This non-randomized cross-sectional observation study was conducted from July 2021 to April 2023, comparing two cohorts of patients with confirmed or suspected long COVID. The EECP group consisted of patients who were referred to Flow Therapy centers throughout Texas, Arizona, and North Carolina for the management of long COVID symptoms, who each completed 25–45 sessions of EECP therapy over a 7-week period. The control cohort (non-treated group) consisted of patients who had taken the standardized validated assessments available on the Flow Therapy website two times, approximately 7 weeks apart, but did not undergo EECP. This study was approved by the Institutional Review Board at the University of the Pacific (IRB2022-65).

2.2. EECP Treatment

A full course of EECP consists of 1-h sessions 5 days per week for 7 weeks, totaling 35 sessions. Some patients completed only 25 sessions due to tolerability or time constraints, and some completed 45 sessions as the referring provider can recommend an extra 10 sessions upon completion of the full course if the patient requires additional symptomatic relief. During therapy, patients lie on a padded treatment bed with 3 sets of pneumatic cuffs wrapped around the lower extremities. The cardiac cycle is monitored by a 3-lead ECG with inflation of the cuffs timed to occur during diastole and deflation occurring just prior to the onset of systole [10].

2.3. Inclusion and Exclusion Criteria

Patients were included in the EECP group if they were referred to Flow Therapy for the management of long COVID symptoms and completed the validated symptom assessments both pre- and post-therapy. Individuals in the control group suspected they had long COVID (it is unknown whether they were seeing any provider for diagnosis or management) and were included if they completed the assessments twice between 5 and 12.29 weeks apart. Patients were excluded from the control group if, after conducting the matching process, they did not have a match in the treated group.

2.4. Matching

The two groups were matched according to baseline characteristics in a sequential manner. The algorithmic approach first involved matching pairs for sex, and all pairs were an exact match. Next, pairs needed to fall within the same age range (30–39, 40–49, 50–59, or 60+) as an exact match. The amount of time between taking the assessments pre- and post-therapy (e.g., 7 weeks) needed to be within a one-week time frame difference to match. Finally, baseline PROMIS Fatigue severity needed to fall within the same category (normal, mild, moderate, or severe) as an exact match. After taking all the previous criteria into account, the closest match for DASI and RDS was subsequently considered.

2.5. Endpoints

The following validated assessments were analyzed: Patient Reported Outcome Measurement Information System (PROMIS) Fatigue (short form 4a), DASI, and RDS. PROMIS Fatigue assesses a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in familial or social roles. T-scores range from 20 to 80, with higher scores indicating worse fatigue [15]. DASI, a measure of cardiopulmonary functional capacity, has a score ranging from 0 to 58.2, with higher scores indicating greater levels of fitness [16]. RDS, a symptom-specific measure of dyspnea level during activity, has scores ranging from 0 (no dyspnea) to 4 (severe limitation of physical activity due to dyspnea) [17]. Both cohorts completed the same clinically validated tools twice. The EECP group took the assessments pre- and post-7-week therapy. The control group took the assessments with approximately 7 weeks in between each assessment.

Additionally, we determined a 3-point composite endpoint composed of fatigue (PROMIS Fatigue T-Score), functional capacity (DASI), and dyspnea (RDS). The percentage of patients improving in a clinically significant manner in all three of these markers concurrently was also assessed. Clinical significance was defined as a change from the baseline in PROMIS Fatigue by $\geq$10 points [15], DASI by $\geq$4 points [18], and RDS by $\geq$1 point, in accordance with prior studies [17].

2.6. Data Analysis

Differences between the EECP group and the control group were assessed using chi-square and Fisher's exact tests for categorical data. Continuous variables were assessed for normality using the Shapiro–Wilk test, and Student's *t*-test and Wilcoxon's rank-sum test were used to assess differences between groups depending on the distribution. Intra-group changes between pre- and post-assessment periods were assessed using a paired *t*-test or Wilcoxon signed-rank test where appropriate for continuous data, while changes in the categorical variable of severe dyspnea were assessed using the exact version of McNemar's test. Analyses were performed in Stata, version 17.0 (Statacorp, College Station, TX, USA).

3. Results

After conducting the matching process from a cohort of 231 patients with long COVID having undergone EECP, 33 matched pairs were available for analysis as the control group.

The patients in the EECP and non-treated groups were well matched at baseline for age (57 (48, 65) vs. 55 (45, 65) years), gender (72.7% female in both groups), time since acute COVID-19 infection (7.5 (5.7, 16.6) vs. 8.8 (3.6, 11.7) months), and time between pre- and post-assessment periods (7.3 ± 1.3 vs. 7.1 ± 1.3 weeks), respectively (Table 1).

Table 1. Baseline characteristics.

Parameter	N	EECP Group	N	Control Group	*p*-Value
Age in years, median (IQR)	33	57 (48, 65)	33	55 (45, 65)	0.574
Gender, % female	33	72.7	33	72.7	1.0
Time since COVID-19 infection, months, median (IQR)	33	7.5 (5.7, 16.6)	33	8.8 (3.6, 11.7)	0.841
Duration between pre- and post-assessment periods, weeks, mean ± SD	33	7.3 ± 1.3	33	7.0 ± 1.3	0.510
PROMIS Fatigue T-Score, mean ± SD	33	67.2 ± 7.2	33	67.2 ± 6.5	0.984
DASI, median (IQR)	33	10.0 (4.5, 13.5)	33	7.2 (2.7, 18.7)	0.841
RDS, median (IQR)	33	3 (2, 4)	33	3 (2, 4)	0.640

SD: standard deviation; DASI: Duke Activity Status Index; RDS: Rose Dyspnea Scale.

Patients in the EECP group had significant improvements across all endpoints when compared to their baseline and the non-treated group (Table 2). When comparing the average change from baseline in PROMIS Fatigue in both groups, the EECP group's improvement was significantly greater than the improvement in the non-treated group (−15.0 ± 8.9 vs. −2.8 ± 5.9, respectively; $p < 0.001$) (Table 2). The change from baseline in the DASI was +17.8 (11.8, 26.8) vs. +1.8 (−3.5, 5.5) ($p < 0.001$) in the EECP and non-treated groups, respectively. The change from baseline in the RDS was −1.5 ± 1.3 vs. −0.2 ± 0.9 ($p < 0.001$) in the EECP and non-treated groups, respectively. A total of 28 (84.9%) patients in each group had severe dyspnea (RDS ≥ 2) at baseline, while 15 (45.5%) in the EECP group and 26 (78.8%) in the non-treated group had severe dyspnea at the post-assessment period. This represents a significant improvement among the EECP group ($p = 0.001$). When analyzing changes in RDS class, 25 patients (75.8%) in the EECP group compared to 11 patients (33.3%) in the non-treated group had an improvement of ≥1 class ($p = 0.001$).

Table 2. Changes in PROMIS Fatigue, DASI, and RDS.

Parameter	Cohen's *d*	N	EECP Treatment Group	N	Control Group	*p*-Value
PROMIS Fatigue						
Average change from baseline	1.62	33	−15.0 ± 8.9 *	33	−2.8 ± 5.9 *	<0.001
DASI						
Median change from baseline	2.18 ^	33	+17.8 (11.8, 26.8) *	33	+1.8 (−3.5, 5.5)	<0.001
RDS						
Improvement of ≥1 in RDS Class, n (%)		33	25 (75.8)	33	11 (33.3)	0.001
3-Point Composite						
Clinically meaningful improvement in all 3 endpoints, n (%)		33	18 (54.6)	33	0 (0.0)	<0.001

* indicates significant change from baseline (all *p*-values, $p < 0.02$). DASI: Duke Activity Status Index; RDS: Rose Dyspnea Scale. ^ For non-normally distributed data, η2 was calculated and then transformed to estimate Cohen's *d*.

When using the three-point composite endpoint to assess clinical significance simultaneously across all three endpoints (PROMIS Fatigue, DASI, and RDS), 54.6% of patients had a clinically significant improvement in the EECP group, whereas in the non-treated group, none of the patients had an improvement [Table 2] ($p < 0.001$).

4. Discussion

This is the first study showing significant improvements in fatigue, dyspnea, and functional capacity in patients with long COVID undergoing EECP relative to a non-treated

group, confirming our hypothesis. We demonstrated that over half of the patients in the EECP group had a clinically significant improvement in all three symptom measures as opposed to no patients in the non-treated control group.

The magnitude of benefit when utilizing EECP as a long COVID treatment strategy was significant. EECP treatment led to a 17.8-point improvement in DASI, which is almost double the average improvement in the DASI of 9.2 that was observed in a recent study involving 601 participants with long COVID who underwent an exercise rehabilitation and emotional wellbeing program [19]. The between-group difference in PROMIS Fatigue >11 is notable as changes >3 points are considered clinically meaningful [15]. More than double the number of patients who underwent EECP had an improvement in the RDS of $\geq$1 class, an independent predictor of all-cause and cardiovascular mortality [20].

The pathophysiology of long COVID is complex, with evidence suggesting that immune dysregulation and endothelial and microvascular dysfunction—known mechanisms by which EECP leads to improved symptoms—have roles [21]. Endothelial dysfunction is associated with suppressed endothelial nitric oxide synthase and concomitant nitric oxide (NO) deficiency and is thought to play a key role in long COVID [22,23]. Studies have demonstrated that many of the PASC manifestations can be attributed to vascular endothelial injury and subsequent dysfunction [24]. In a recent analysis by Mclaughlin et al., patients with long COVID had significantly lower flow-mediated dilation (FMD) compared to the controls (6.99 $\pm$ 4.33% vs. 11.30 $\pm$ 4.44%, p = 0.022) [25]. EECP has the potential to target these pathophysiologic mechanisms of long COVID [26]. By increasing pulsatile diastolic coronary perfusion and endothelial shear stress [27], EECP treatment results in the suppression of many inflammatory biomarkers, stimulates angiogenesis, and leads to improved endothelial and microvascular function [28] and immune regulation [29]. A randomized sham-controlled study by Braith et al. demonstrated that in patients with stable angina, EECP significantly improved brachial and femoral artery FMD, increased the bioavailability of NO, and decreased the levels of plasma biomarkers of inflammation, vasoconstriction, and oxidative stress [30]. CMD is implicated in the pathogenesis of long COVID [31]. Our recent study in 101 patients with angina and non-obstructive coronary artery disease diagnosed with CMD showed significant improvements in the Seattle Angina Questionnaire (SAQ), Canadian Cardiovascular Society (CCS) class, Six Minute Walk Test (6MWT), and DASI post-EECP treatment [32]. Similarly, a pilot study by Wu et al. that included 10 patients with CMD undergoing a modified EECP course (15 one-hour sessions over five weeks) showed significant improvement in exercise tolerance, angina, fatigue, depression, and health-related quality of life [14].

The limitations of the current study include the small sample size, lack of information regarding concurrent treatments or interventions, and an incomplete history of patient comorbidities. A recent report on long COVID and self-management highlights that people living with long COVID are turning to a vast range of over-the-counter medicines and supplements and incorporating dietary changes in attempts to mitigate symptoms [5]; as such, it is plausible that the non-treated group used therapies that we were unaware of. In addition, this study was non-randomized. Further research, particularly a randomized controlled clinical trial, is warranted to confirm our findings.

5. Conclusions

In conclusion, EECP improved long COVID-associated fatigue and cardiopulmonary symptoms relative to a matched control group. Despite the limitations, this is the first comparison of patients with long COVID undergoing EECP versus those not receiving EECP therapy, with significant benefits being evidenced. The disability and morbidity associated with post-COVID complications, in addition to the current lack of effective and reimbursable interventions, can lead to decreased productivity and workforce participation. As patients continue to live with symptoms for months and years post-COVID-19 infection, there is an urgent need for coordinated national health policy action to investigate poten-

tial strategies. The magnitude of this benefit is clinically important, warranting a larger randomized controlled trial.

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Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflicts of Interest: J.F. is an employee of Flow Therapy. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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