Brief report

Enhanced External Counterpulsation Improves Long COVID−Associated Symptoms

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Long COVID, or postacute sequelae of COVID-19, constitutes a substantial global health burden and is associated with social and family-life disturbances, including adjusted workloads and loss of employment.[1] Recent studies report the most prevalent symptoms are fatigue, chest pain, shortness of breath, and memory impairment and highlight the need to identify clear treatment options.[2] Enhanced External Counterpulsation (EECP) is a noninvasive outpatient treatment that is Food and Drug Administration (FDA) −approved for the management of refractory angina and ischemic heart failure and has evidence supporting its use in conditions that occur as a result of vascular inflammation and/or endothelial dysfunction[3]—key factors in the pathophysiology of long COVID. A recent study reported that dysregulation of vascular endothelial cells and angina or ischemia with no obstructive coronary arteries (ANOCA/INOCA) are likely major contributors to long COVID symptoms.[4] EECP has shown to benefit the population with ANOCA/INOCA and leads to an increase in vascular endothelial progenitor cells.[5,6] Therefore, EECP is a rational treatment modality for long COVID and warrants further investigation in this challenging patient population. We present the largest cohort to date of patients diagnosed with long COVID by a referring provider and treated with EECP. This retrospective study was approved by the institutional review board at the University of the Pacific. Changes from baseline in the Seattle Angina Questionnaire (SAQ7), Canadian Cardiovascular Society (CCS) class, PROMIS fatigue, Duke Activity Status Index (DASI), 6-Minute Walk Test (6MWT), and Rose Dyspnea Scale (RDS) were evaluated using a paired Student's *t* test to compare the intergroup differences and an unpaired *t* test for intragroup comparisons. Fisher's exact test was used to analyze the differences in categorical variable severity (CCS and RDS) before and after EECP. A total of 231 patients were included for analyses, with an average age of 52.9 ± 14.4 years, 59.7% women, an average of 8.7 ± 6.2 months since most recent acute COVID-19 infection, and underwent an average of 32.5 ± 4.4 sessions of EECP. Past medical history included hypertension (41.6%), dyslipidemia (41.6%), heart failure (23.8%), diabetes (21.7%), and asthma (20.4%). Current or former smoking status was present in 26.7% of patients. COVID-19 history included 46.7% of patients having received at least 1 dose of the COVID-19 vaccine, 29.5% vaccinated at the time of acute infection, only 22.5% previously hospitalized because of COVID-19, and 9.7% having been infected with SARS-CoV-2 more than once. Long COVID−related symptoms included fatigue (99.1%), dyspnea (94.4%), brain fog (78.8%), chest pain (66.7%), and dizziness (44.2%). As listed in Table 1, there were significant improvements after EECP in SAQ7 by +19.8 ± 21.1, PROMIS fatigue by −13.2 ± 9.7, DASI by +20.8 ± 14.7, and 6MWT by +151.6 ± 199.1 ft (all $p < 0.001$). In addition, 54.8% of patients had moderate to severe angina (CCS class 3 or 4) at baseline, with only 17.5% having moderate to severe angina after EECP ($p < 0.001$), and 88.2% of patients experienced an improvement in at least 1 CCS class. The percent of patients with moderate to severe dyspnea (RDS classes 2 to 4) at baseline was 84.9%, which improved to 35.9% after EECP ($p < 0.001$). Of the patients subjectively reporting the symptom of brain fog, a significant number self-reported improvements in their cognitive symptoms (90.3% compared with 9.7% who reported no change, $p < 0.001$). In addition, 23 patients (10%) reported being unable to work because of their symptoms. Of these, 18 patients (78.3%) returned to work after EECP ($p < 0.001$). Throughout the duration of this study, patients underwent a cumulative total of 7,296 hours of EECP treatments, with no documented safety concerns, including no incident reports and no utilization of emergency services. In the largest patient series to date, we provide foundational evidence supporting the role of EECP in the management of long COVID. Our demographic data are consistent with previous findings that women make up approximately 60% of the long COVID population and 76% of patients diagnosed with long COVID were not hospitalized during their acute COVID-19 infection.[7] A recent 2 year follow-up of more than 6 million participants highlighted the substantial cumulative burden of health loss because of long COVID, impacting quality of life (QoL), labor participation, economic productivity, and societal well-being.[8] Our study shows that EECP improved QoL and allowed a significant proportion of patients to return to work (78%). The pathophysiology of long COVID

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Table 1
Change in validated scores after EECP therapy

Parameter	N	Pre-EECP	Post-EECP	Delta	p-value
SAQ7	230	65.07±26.50	84.84±17.15	+19.77±21.12	<0.001
PROMIS Fatigue	231	66.28±7.86	53.06±9.17	-13.22±9.65	<0.001
DASI	231	12.49±12.04	33.19±16.25	+20.79±14.73	<0.001
6MWT (feet)	221	1200.66±401.98	1351.45±397.55	+151.62±199.05	<0.001
Mod/Sev Angina (%)	217	54.84	17.51	-37.33	<0.001
Mod/Sev Dyspnea (%)	231	84.85	35.93	-48.92	<0.001

symptoms is multifactorial but includes inflammation and endothelial or coronary microvascular dysfunction.[4] Treatment with EECP has demonstrated, in a randomized, sham-controlled study, decreased levels of inflammatory markers and increased flow-mediated dilation, an indicator of endothelial function improvement.[9] A recent study by Wu et al[10] included patients with coronary microvascular dysfunction who underwent EECP and showed improvement in exercise capacity, fatigue, and health-related QoL, and a recent analysis of 101 patients with ANOCA who underwent EECP showed significant improvements in SAQ7, CCS class, 6MWT, and DASI after EECP.[5] Similarly, the results of our study showed significant improvement in fatigue, angina, dyspnea, and exercise capacity in patients with long COVID. The limitations of this study include that long-term follow-up was not performed; therefore, how long the benefits are sustained remains unknown and the concurrent use of other interventions for long COVID cannot be ruled out. The lack of a control group is the major limitation; however, these results provide promising safety and efficacy data for EECP in managing long COVID, providing the foundation for a randomized clinical trial. EECP appears to be particularly attractive given the multimodal mechanism of action and evidence of significant improvement across multiple symptoms. This preliminary analysis shows that treatment with EECP led to significant improvement in long COVID using validated markers, which collectively assess symptoms most prevalent in patients with long COVID. A controlled clinical trial is warranted to further authenticate these findings.

Declaration of competing interest

Dr. Fox is an employee of Flow Therapy. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Jessie Fox: Writing − review & editing, Writing − original draft, Methodology, Investigation, Formal analysis. **Monica Verduzco-Gutierrez:** Project administration, Formal analysis, Data curation, Conceptualization. **Steven Sanchez:** Visualization, Validation, Supervision, Software, Resources. **Marielisa Lopez:** Visualization, Validation, Resources, Project administration. **Farhan Ali:** Supervision, Software, Project administration, Investigation. **Odayme Quesada:** Writing − review & editing, Writing − original draft, Visualization, Validation. **Timothy D. Henry:** Writing − review & editing, Writing − original draft, Visualization, Project administration, Methodology. **Sachin A. Shah:** Writing − review & editing, Writing − original draft.

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