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Original Article

EECP improves markers of functional capacity regardless of underlying ranolazine therapy

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Abstract: Objective: Enhanced external counterpulsation (EECP) and ranolazine are approved treatments for patients with chronic stable angina by the United States Food and Drug Administration (FDA). Whether EECP offers clinical benefits regardless of underlying ranolazine therapy needs further investigation. Methods: This was a retrospective evaluation of patients referred to a specialized EECP center. Patients having data on 6-Minute Walk Distance (6MWD) or Duke Activity Status Index (DASI) were categorized into two groups (EECP with ranolazine or EECP only). The primary endpoints were change in 6MWD and DASI before and after a full course of EECP within each of the two groups. Inter-group differences were also assessed. The Wilcoxon test was utilized to compare the change from baseline within each group and the Mann-Whitney U test to compare difference between groups. Results: A total of 2836 patient records (age 66.9 ± 10 years) were identified (1193 in EECP and ranolazine group and 1643 in EECP only group). EECP added to baseline ranolazine resulted in a statistically significant improvement in 6MWD and DASI (+126 feet (IQR: 230 feet), and +13.35 (IQR: 17.11), respectively, P<0.001 for both). Similarly, the EECP only group showed a statistically significant improvement in 6MWD and DASI (+140 feet (IQR: 225 feet) and +13.49 (IQR: 18.02), respectively, P<0.001 for both). There was no statistically significant difference between the two groups when comparing the change from baseline in 6MWD and DASI score (P=0.256 and P=0.056 respectively). Conclusion: EECP improves markers of functional capacity regardless of baseline ranolazine therapy. EECP's unique safety profile advocates for its early consideration in the treatment algorithm.

Keywords: EECP, ranolazine, chronic stable angina, functional capacity, quality of life

Introduction

In the United States, 9.4 million people over the age of 20 suffer from angina [1]. Class I recommendations for the management of chronic stable angina (CSA) include pharmacologic interventions such as beta-adrenergic blockers, calcium channel blockers, and nitrates along with invasive modalities including percutaneous coronary interventions (PCI) and coronary artery bypass grafts (CABG) [2]. Despite optimized pharmacotherapy and surgical interventions, refractory angina affects an estimated 600000 to 1.8 million people within the United States with an approximate 50000 to 100000 newly diagnosed cases each year [3]. This population has a high incidence of hospitalization secondary to their burden of disease with an estimated average cost of $10080 per hospitalization [4].

Ranolazine is approved by the United States Food and Drug Administration (FDA) as add-on therapy to Class I agents for the treatment of CSA (Class IIa, level B) [2, 5]. Enhanced external counterpulsation (EECP) is an FDA approved non-invasive device for treatment of patients with chronic stable angina or heart failure (Class IIb, level B) [2]. A full course of EECP therapy typically consists of 1-hour sessions 5 days per week for 7 weeks, totaling 35 sessions [2, 6].

EECP treatment is relatively well tolerated with side effects primarily related to device use [7]. Multiple studies have found that EECP improves markers of functional capacity such as 6-Minute Walk Distance (6MWD) and Duke Activity Status Index (DASI) [8, 9]. While these results are promising, they are limited by small study populations (under 200 patients) and

have yet to explore the isolated degree of benefit from EECP when added to baseline ranolazine therapy [10]. EECP therapy is one of only two guideline supported non-pharmacologic treatment modalities that mechanistically improves myocardial perfusion to relieve symptoms of refractory angina [11]. With the generic availability of ranolazine as of February 2019 and emerging data supporting the clinical use of non-pharmacologic treatments like EECP, understanding the magnitude of benefit EECP has when added to ranolazine therapy is particularly warranted [11, 12]. The intent of our study was to investigate whether EECP offers clinical benefits independent of underlying ranolazine therapy.

Methods

Study design

This retrospective analysis was approved by the Institutional Review Board at the University of the Pacific. All patients receiving care at Flow Therapy clinics with a diagnosis of angina from April 2013 to October 2018 with data on 6MWD and DASI were eligible for inclusion in the analysis (n=2836 records).

Patients were allocated into either the EECP and ranolazine (EECP+R) or EECP only groups according to baseline ranolazine usage. Patients were included if they had pre- and post-data on 6MWD or DASI. Data was extracted from the outpatient clinic's electronic health record with a Python script (Python version 3.7) written to extract the following data: patient identification, age, gender, comorbidities, baseline medications, pre- and post-6MWD (feet), pre- and post-DASI, and baseline CCS angina class.

The pre-specified primary endpoints were changes from baseline in 6MWD and DASI after a full course of EECP treatment in patients with and without ranolazine therapy. The 6MWD is validated measurement of exercise functional capacity commonly used to assess responses to medical interventions in patients suffering from chronic cardiovascular and pulmonary diseases [13, 14]. The 6MWD is a strong predictor of cardiovascular events in patients with stable coronary heart disease and an independent measure of morbidity and mortality amongst patients suffering from congestive heart failure and chronic obstructive pulmonary disease [11, 15]. The test measures the distance patients are able to walk on a flat, hard surface in a duration of 6 minutes and is a predictor of health outcomes in stable coronary heart disease, heart failure, pulmonary hypertension, and pulmonary disease [13, 14]. The DASI is a validated 12 item questionnaire used to measure health-related quality of life specific to cardiovascular functional status [12-14]. The questionnaire provides independent prognostic information for long-term adverse clinical events in stable cardiac patients, as well as an indicator of mortality in patients with chronic heart failure [15-17]. Due to the retrospective nature of this analysis, all patients treated with a full course of EECP and not on baseline ranolazine therapy were considered as a comparator group.

Patients who visited the center for multiple treatment courses were included in the overall analysis. Patients not completing at least 30 EECP sessions were excluded from analyses. A sensitivity analysis was performed to assess changes in the primary endpoints in patients having gone through only 1 full course (1 round) of EECP, having a baseline Canadian Cardiovascular Society (CCS) angina class ≥3 or with heart failure.

Statistical analysis

We performed the Wilcoxon test to compare the change from baseline within each group (intra-group) and the Mann Whitney U-test was utilized to compare the changes from baseline in the EECP+R and EECP only groups (inter-group). A $P<0.05$ was considered statistically significant. A Fisher's exact was performed to assess differences in categorical variables. All data are represented as median and interquartile range. All analysis was done using Python script (Python version 3.7).

Results

Baseline demographics

A total of 2836 patient records were identified having available data for 6MWD or DASI (1193 (42.1%) in the EECP+R group and 1643 (58.0%) patients in the EECP only group). Of those enrolled 2312 unique patients completed only one course of EECP. Overall, patients were predominantly male (70.0%) with an aver-

Table 1. Baseline demographics

Demographic	EECP+R (n=1193)	EECP Only (n=1643)
Average Age	66.0 ± 11	67.6 ± 10
Male	838 (70%)	1144 (70%)
CABG	715 (60%)	818 (50%)
PCI	396 (33%)	522 (32%)
CAD	1174 (98%)	1612 (98%)
Diabetes	591 (50%)	722 (44%)
Heart Failure	385 (32%)	654 (40%)
Hyperlipidemia	997 (84%)	1363 (83%)
Hypertension	1091 (92%)	1459 (89%)
Myocardial Infarction	591 (50%)	760 (46%)
6MWD	1175 ± 381	1105 ± 390
DASI	9.7 ± 10	10.3 ± 15
ACE Inhibitors	412 (35%)	540 (33%)
ARB	310 (30%)	402 (25%)
Alpha blockers	39 (3%)	44 (3%)
Aspirin	988 (83%)	1236 (75%)
Blood Thinner†	790 (66%)	945 (56%)
Beta blockers	956 (80%)	1246 (76%)
Calcium Channel Blockers	342 (29%)	421 (26%)
Digoxin	28 (2%)	56 (3%)
Diuretics	439 (37%)	683 (42%)
Nitrates	994 (83%)	974 (59%)
Omega Fatty Acids	213 (18%)	232 (14%)
Statins	988 (83%)	1280 (78%)

ACE inhibitor, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II receptor blockers; 6MWD, 6-Minute Walk Distance; CABG, Coronary Artery Bypass Grafts; CAD, Coronary Artery Disease; CCS, Canadian Cardiovascular Society; DASI, Duke Activity Status Index; EECP, Enhanced External Counterpulsation; EECP+R, EECP and Ranolazine Group; PCI, Percutaneous Coronary Interventions. †including antiplatelet agents (ticagrelor and prasugrel) and direct oral anticoagulants (apixaban and rivaroxaban).

age age of 66.9 ± 10. Of the patients included 98.2% had coronary artery disease (CAD), 36.6% had heart failure, 46.3% had diabetes, 83.2% had concomitant hyperlipidemia, and 89.9% had hypertension. Nearly 42.0% (n= 1193) of the overall cohort were on ranolazine therapy at baseline (**Table 1**).

Outcomes in EECP+R Group

Post EECP therapy, all patients on baseline ranolazine (EECP+R group) showed a statistically significant improvement in 6MWD (+126 ft (IQR 230), P<0.001) and DASI (+13.35 (IQR 17.11), P<0.001). When limiting the model to patients completing 1 round only, statistically significant improvements were shown in 6MWD (+125 ft (IQR 230), P<0.001) and DASI (+13.5 (IQR 18.45), P<0.001). Further, patients with a CCS angina class ≥3 also demonstrated significant improvements in 6MWD (+130 ft (IQR 230), P<0.001) and DASI (+13.44 (IQR 17.04), P<0.001). Likewise, when limited to patients with heart failure, results maintained significance for each of the study end points (6MWD +135 ft (IQR 249), P<0.001 and DASI +11.49 (IQR 16.25), P<0.001). **Figures 1** and **2** describe the change in 6MWD and DASI for the EECP+R and EECP only groups.

Outcomes in EECP only group

The EECP only cohort similarly showed a statistically significant improvement in 6MWD (+140 ft (IQR 225), P<0.001) and DASI (+13.49 (IQR 18.02), P<0.001). In participants completing 1 round only, improvements in 6MWD (+140 ft (IQR 225), P<0.001) and DASI (+13.56 (IQR 18.45), P<0.001) were also statistically significant. Statistical significance was maintained when limiting analysis to CCS angina class of ≥3 (6MWD +140 ft (IQR 225), P<0.001 and DASI +13.49 (IQR 18.01), P<0.001). Similarly, improvements in 6MWD (+135 ft (IQR 235), P<0.001) and DASI (+11.69 (IQR 17.85), P< 0.001) were statistically significant when limited to patients with heart failure.

Outcomes comparing EECP+R vs. EECP only groups

There were no statistically significant differences for 6MWD and DASI between the EECP+R and EECP only groups (P=0.2560 and P=0.0558 respectively) (**Table 2**). This was true across all subgroups for both endpoints (all *p*-values >0.05).

Discussion

Our findings indicate EECP therapy improves markers of functional capacity regardless of baseline ranolazine therapy. These benefits were maintained after limiting the analysis to participants completing only 1 course of EECP, having CCS angina class of ≥3, or having heart failure.

The magnitude of change for 6MWD (>125 ft) is clinically meaningful. Generally, improvements ranging from 82 ft (25 m) to 229 ft (70 m) in 6MWD are associated with enhanced

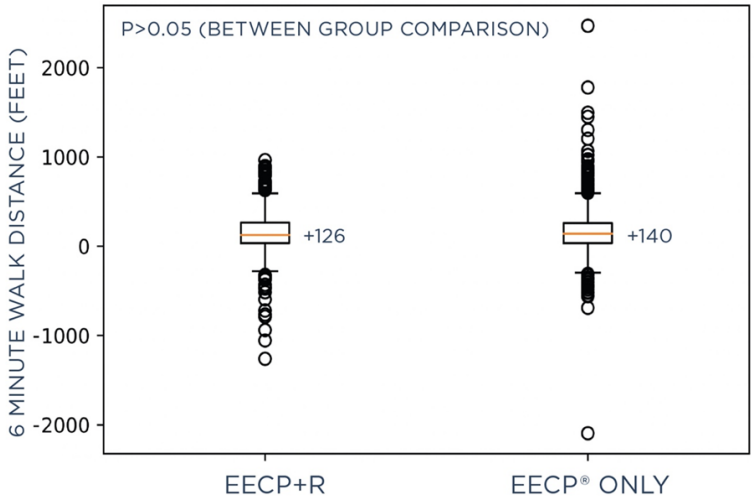

Figure 1. Improvement from baseline in 6MWD for EECP+R and EECP only. Patients in the EECP+R group showed a statistically significant improvement in 6MWD of +126 ft (IQR 230) with P<0.001 from baseline. Likewise, patients in the EECP only group showed a statistically significant improvement from baseline in 6MWD of +140 ft (IQR 225) with P<0.005. The intergroup analysis between the two groups was not statistically significant (P>0.05). Abbreviations: 6MWD, 6-Minute Walk Distance; EECP, Enhanced external counterpulsation; EECP+R, EECP and ranolazine.

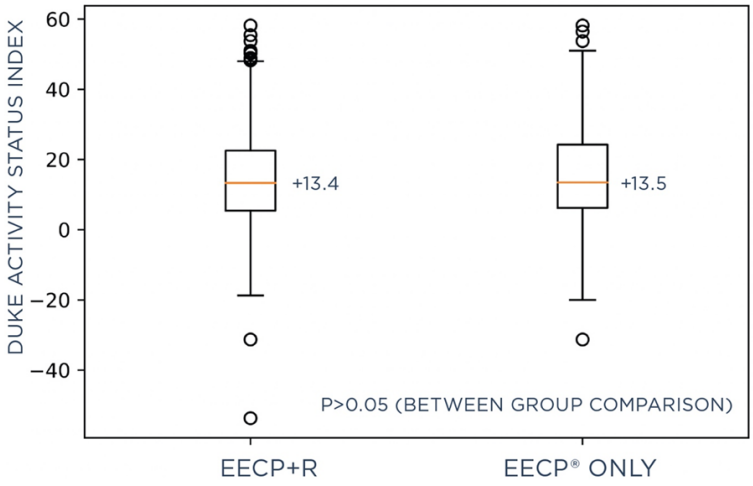

Figure 2. Improvement from baseline in DASI for EECP+R and EECP only. Patients in the EECP+R group had a statistically significant improvement from baseline DASI score of +13.35 (IQR 17.11) with P<0.001. Patients in the EECP only cohort also showed a statistically significant improvement in DASI of +13.49 (IQR 18.02) with a P<0.001. Intergroup analysis did not show a statistically significant difference in improvement in DASI (P>0.05). Abbreviations: DASI, Duke Activity Status Index; EECP, Enhanced external counterpulsation; EECP+R, EECP and ranolazine.

clinical outcomes and mortality benefits [13, 18, 19]. A study conducted by Beatty et al found that in patients with stable coronary heart disease, each standard deviation reduction in 6MWD (341 ft [104 m]) was associated with a 54% higher risk of death (age-adjusted HR 1.54, 95% CI 1.32-1.80) and a 55% increased risk of any cardiovascular event (age-adjusted HR 1.55, 95% CI 1.35-1.78) [14].

The improvement in DASI in both groups was approximately 13 points. A change of 4-6 points in DASI score is associated with improved clinical outcomes [20-22]. A study evaluating the prognostic value of the DASI on 1700 stable, non-acute coronary syndrome patients with heart failure found that DASI scores in the lowest quartile were at a 3.3 fold increased risk in 5 year mortality as compared to the highest score quartile (HR 3.33, 95% CI 2.57-4.36, P< 0.0001) [23].

Our results parallel previous findings showing EECP's independent improvement in markers of functional capacity. A prospective, longitudinal pilot study by Wu et al, assessed changes from baseline in 6MWD 6 months post EECP therapy in 34 patients with refractory angina. They found 6MWD improved from 1345 ft (410 m) at baseline to 1440 ft (439 m) (P<0.01) post treatment (+95 ft (29 m)). The change evident in our EECP only group is higher than that observed by Wu et al; this may be due to our patient population being at a lower baseline functional capacity, the low sample size in the study by Wu et al, or better EECP care provided by the particular centers in our analyses [8]. EECP has also shown independent positive effects on DASI scores. A prospective analysis of 13 patients with chronic stable angina found that after completion of a full course of EECP therapy there were marked improvements in DASI scores (12 ± 2 vs. 19 ± 3; P=0.03) [9].

Table 2. Change in markers of functional capacity

Population	N	Change in EECP+R, Median (IQR)	N	Change in EECP Only, Median (IQR)	*P*-value
6MWD (feet)					
All Patients	1104	126 (230)	1545	140 (225)	0.256
Round 1 Only	859	125 (230)	1305	140 (225)	0.173
≥3CCS	1033	130 (230)	1401	140 (225)	0.425
HF Only	350	135 (249)	609	135 (235)	0.203
DASI					
All Patients	900	13.35 (17)	1279	13.49 (18)	0.056
Round 1 Only	728	13.50 (18)	1122	13.56 (18)	0.130
≥3CCS	845	13.44 (17)	1164	13.49 (18)	0.061
HF Only	293	11.49 (16)	499	11.69 (17)	0.330

CCS, Canadian Cardiovascular Society; DASI, Duke Activity Status Index; EECP, Enhanced external counterpulsation; EECP+R, EECP and ranolazine; HF, heart failure; IQR, Interquartile Range; 6MWD, 6-Minute Walk Distance.

For comparison, ranolazine added to standard of care therapy improves 6MWD and DASI by 37.7 ft (11.5 m) (992.5 ft (302.5 m) ± 423.2 ft (129.0 m) baseline to 1030.2 ft (314.0 m) ± 418.3 ft (127.5 m) at 12 months) and 3.8 points (18.7 ± 14.9 baseline to 22.5 ± 15.8 at 12 months) respectively. These results were not found to be statistically significant for either endpoint [24, 25].

The magnitude of benefit seen in our results can be explained by the fact that ranolazine and EECP have differing mechanisms of action. EECP's mechanism of action is similar to an intra-aortic balloon pump where inflation and deflation of the pneumatic cuffs during diastole and systole are synchronized to heart rhythm. This results in an increase in coronary diastolic pressure and improved oxygen supply with retrograde aortic blood [26]. It is postulated that benefits observed with EECP therapy may be secondary to development of new collateral blood vessels, improved endothelial function and vascular reactivity, and enhanced ventricular function [17, 27-29]. In contrast, ranolazine is a piperazine derivative that inhibits late sodium channels in myocardial tissue. While the exact mechanism of action of ranolazine is not fully realized, it has been known to impede myocardial sodium overload leading to improved myocardial relaxation, reduced ventricular rigidity, and subsequent improved myocardial perfusion [30]. Ranolazine does not appear to effect heart rate or blood pressure [31]. Our findings are not too surprising as based on a recent meta-analysis from the Cochrane Library, ranolazine add-on therapy only improved angina frequency and did not provide any mortality or quality-of-life benefits [32].

To our knowledge, this is the largest analysis comparing the addition of EECP to ranolazine and raises the question of EECP's role in the treatment of refractory angina. Elective surgical revascularization is a high cost and invasive procedure that while proven to improve coronary ischemia, does not provide superior results to medical optimization. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial (COURAGE), PCI added to optimized medical therapy did not reduce the risk of death or myocardial infarction in patients with objective myocardial ischemia and coronary artery disease in comparison to patients receiving only optimized medical therapy [33]. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes study (BARI 2D), CABG or PCI added to optimized medical therapy was found to be equivalent to optimized medical therapy in reducing the risk of death or major adverse cardiovascular events (MACE) (death, MI, or stroke) [34]. The Percutaneous Coronary Intervention in Stable Angina trial compared PCI to placebo in medically optimized patients with angina. The study found that PCI did not improve treadmill exercise time as compared to placebo (16.6 s, 95% CI -8.9-42, P=0.20) [35].

More recently, in the landmark study International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) 5179 participants with stable ischemic heart disease and moderate or severe ischemia on stress imaging or severe ischemia based on non-imaging exercise tolerance test-

ing were randomized to receive optimal medical therapy or invasive surgical revascularization. The study results showed that initial invasive intervention, as compared to optimized medical therapy, did not demonstrate a reduction in the study's primary end point of time to cardiovascular death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest (Adjusted HR invasive vs. conservative 0.93 (0.80, 1.08); P=0.34) [33]. In our analysis we found that even patients on baseline ranolazine had clinical benefits from the addition of EECP. Our results further support the early consideration of EECP for patients with stable ischemic heart disease. As such, it is plausible that EECP may provide enough benefits to eliminate the addition of further pharmacotherapeutic options in a population with a pre-existing high pill burden.

Medication non-adherence in patients with cardiovascular disease varies from 24% to 60%, and as a result one potential drawback to ranolazine use in patients with refractory angina is that treatment requires long term medication adherence [36-39]. Similarly, compliance with the 35 sessions of EECP is not feasible for all patients. However, after a full course of EECP clinical benefits have been known to sustain for up to 2 years. A long-term clinical outcomes trial showed sustained reductions in CCS angina class in 55% of patients presenting at the two year follow up [6]. While medication optimization remains the primary treatment for angina, using EECP earlier in the treatment algorithm can be a clinically astute strategy in patients especially due to its safety profile and having nearly no contraindications. This application warrants further exploration in future studies.

Though our data suggests that EECP provides clinically meaningful improvements independent of baseline ranolazine use, several limitations need to be considered. While this is the largest analysis of this kind, interpretation is limited by the retrospective study design and lack of propensity score matching. We could not control for background antianginal therapy or medication dose optimization. Since this data was extracted from an outpatient clinic, without access to complete medical records, advanced statistical techniques that control for confounding variables could not be utilized. As such, we accounted for baseline differences between the EECP+R and EECP only groups by comparing the change from baseline rather than the unadjusted absolute values for each endpoint. Future studies would benefit from a ranolazine only arm for comparison.

Conclusion

EECP improves clinically relevant endpoints of 6MWD and DASI by over 125 ft and 13 points respectively. This observed benefit was independent of baseline ranolazine therapy. The observed clinical benefit of EECP is likely driven by its different mechanism of action relative to ranolazine. EECP should be considered earlier in management of angina and ischemic heart disease independent of or complimentary to ranolazine therapy as a result of its superior safety profile, relatively high compliance and sustained long-term benefits.

Disclosure of conflict of interest

The abstract was presented at American Heart Association Scientific Sessions 2019 Conference.

Abbreviations

6MWD, 6-Minute Walk Distance; CABG, Coronary Artery Bypass Grafts; CCS, Canadian Cardiovascular Society; CSA, Chronic Stable Angina; DASI, Duke Activity Status Index; EECP, Enhanced External Counterpulsation; EECP+R, EECP and Ranolazine Group; FDA, Food and Drug Administration; MACE, Major Adverse Cardiovascular Events; PCI, Percutaneous Coronary Interventions.

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