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Efficacy of Enhanced External Counterpulsation in Patients With Chronic Refractory Angina on Canadian Cardiovascular Society (CCS) Angina Class

An Updated Meta-Analysis

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Abstract: A growing number of patients with chronic artery disease suffer from angina, despite the optimal medical management (ie, β -blockers, calcium channel blockers, and long-acting nitrates) and revascularization. Currently, enhanced external counterpulsation (EECP) therapy has been verified as a noninvasive, safe therapy for refractory angina. The study was designed to evaluate the efficacy of EECP in patients with chronic refractory angina according to Canadian Cardiovascular Society (CCS) angina class.

We identified systematic literature through MEDLINE, EMBASE, the Cochrane Clinical Trials Register Database, and the ClinicalTrials.gov Website from 1990 to 2015. Studies were considered eligible if they were prospective and reported data on CCS class before and after EECP treatment. Meta-analysis was performed to assess the efficacy of EECP therapy by at least 1 CCS angina class improvement, and proportion along with the 95% confidence interval (CI) was calculated. Statistical heterogeneity was calculated by I^2 statistic and the Q statistic. Sensitivity analysis was addressed to test the influence of trials on the overall pooled results. Subgroup analysis was applied to explore potential reasons for heterogeneity.

Eighteen studies were enrolled in our meta-analysis. Pooled analysis showed 85% of patients underwent EECP had a reduction by at least one CCS class (95%CI 0.81–0.88, $I^2 = 58.5\%$, $P < 0.001$). The proportion of patients enrolled at primarily different studies with chronic heart failure (CHF) improved by at least 1 CCS class was about 84% after EECP (95%CI 0.81–0.88, $I^2 = 32.7\%$, $P = 0.1668$). After 3 large studies were excluded, the pooled proportion was 82% (95%CI 0.79–0.86, $I^2 = 18\%$, $P = 0.2528$). Funnel plot indicated that some asymmetry while the Begg and Egger bias statistic showed no publication bias ($P = 0.1495$ and 0.2859 , respectively).

Our study confirmed that EECP provided an effective treatment for patients who were unresponsive to medical management and/or invasive

therapy. However, the long-term benefits of EECP therapy needed further studies to evaluate in the management of chronic refractory angina.

(*Medicine* 94(47):e2002)

Abbreviations: CABG = coronary artery bypass graft, CAD = coronary artery disease, CCS = Canadian Cardiovascular Society, CHF = chronic heart failure, CI = confidence interval, DM = diabetes mellitus, EECP = enhanced external counterpulsation, MACE = major adverse cardiovascular events, NO = nitric oxide, PCI = percutaneous coronary intervention.

INTRODUCTION

With the improvements in cardiovascular care, an increasing number of patients, particularly those with advanced coronary artery disease (CAD), have severe symptom of angina pectoris that intractable to treatment of optimal medical therapy. It is estimated that between 600,000 and 1.8 million patients in the United States suffer from chronic refractory angina with about 50,000 new cases emerging per year, and in continental Europe approximately 30,000 to 50,000 new cases are diagnosed each year.¹ Due to the increase of CAD-related survival rate and population age, the incidence and prevalence of these patients will continue to rise. Therefore, the care of these patients is challenging. In order to better manage the population group, the definition of the refractory angina is vital important. The ESC Joint Study Group on the Treatment of Refractory Angina and Canadian Cardiovascular Society (CSS)/Canadian Pain Society Joint Guidelines defined this condition as “chronic duration more than 3 months characterized by the presence of angina caused by coronary insufficiency in the presence of CAD which is refractory to a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery in patients with evidence of ischemia.”^{1,2} As the conventional therapy has limitation, this is an urgent need to search for new treatment for patients. The current therapies of refractory angina including pharmacology (ie, Nicorandil, Ivabradine, Ranolazine, Allopurinol, Perhexiline), noninvasive therapy compromise enhanced external counterpulsation (EECP) and extracorporeal shockwave therapy, invasive therapy, neuromodulation, and others.^{3,4} According to current studies, EECP as a noninvasive therapy has been proven to be a promising treatment for relieving angina, and it has been given II a Class Recommendation in the 2013 ESC guidelines on the management of stable CAD.⁵

EECP therapy, a nonpharmacologic, noninvasive outpatient treatment, has been approved by the U.S. Food and Drug Administration (FDA) in patients with stable or unstable angina

Editor: Yen-Hung Lin.

Received: July 16, 2015; revised: October 14, 2015; accepted: October 16, 2015.

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This work was supported by the National Natural Science Foundation of China (No. 81270175, No.81470404) and the Natural Science Foundation of Shandong Province, China (No.ZR2014HM107).

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002002

pectoris, congestive heart failure, acute myocardial infarction, and cardiogenic shock.⁶ Now this technique is used for patients with angina ineligible to conventional medical therapy who are not candidates for further revascularization procedures and those preferred to delay invasive treatment. Several trials have demonstrated that EECF reduced angina symptom by CCS,^{7–9} improved quality of life,^{8–10} increased exercise capacity^{9–12} as well as enhanced the time to exercise-induced ST-segment depression^{11–13} and to improve myocardial perfusion.^{11,12} In 1 trial, the persistent reduction free of major adverse cardiovascular events (MACE) for up to 5 years treatment.¹⁴

Despite the greatest improvement in treatment modalities for CAD more than 40 years, the data from different observation trials cannot provide strong evidence to prove the effectiveness of EECF. The CCS class of angina severity, ranging from class I to class IV, was widely used in clinic to evaluate activity status and has been recognized as a significant predictor of long-term mortality.¹⁵ The meta-analysis was to assess the efficacy of EECF on CCS angina class in patients with chronic refractory angina.

METHODS

Search Strategy

We searched MEDLINE (source, PubMed, 1990 to March 2015), EMBASE (1990 to March 2015), the Cochrane Clinical Trials Register Database (through March 2015), and the ClinicalTrials.gov Website (through March 2015) using the terms “enhanced external counterpulsation,” “EECF,” and “external counter-pulsation.” No language restriction was performed. In addition, we manually searched the abstracts of annual scientific sessions that relevant to the subject. Potentially relevant articles were then screened by at least 2 independent reviewers; disagreements were resolved by discussion or upon consensus from the 3rd reviewer.

Inclusion and Exclusion Criteria

First, we conducted an initial screening of titles and/or abstracts. Second, reevaluation was performed on the basis of full-text review. The studies were included in our meta-analysis if they met the following criteria: the trial was a prospective design; the trial was conducted in patients with stable angina pectoris; the outcome interest was the adequate data on CCS angina class that reported before and after the 35 1-hour EECF sessions. Although meta-analysis of randomized controlled trials would provide more robust evidence, the feature of the EECF procedure makes it difficult, so the studies that we identified were prospectively planned studies. In order to avoid data duplication and artificial inflation such the sample size, we excluded studies from the International EECF Patient Registry (IEPR) and the EECF consortium. Data unpublished or published as case reports, case series, or abstracts were ruled out unless they met with the inclusion criteria mentioned. In addition, those studies reporting CCS in the form of mean baseline angina class before and after completion EECF treatment were also excluded.

Data Extraction

Data extraction was performed by 2 independent authors (CMZ and XJL) using a standardized data collection form. Disagreements between the reviewers were resolved through discussion or by the 3rd reviewer (XMW). For each

study, the basic characteristics extracted included name of the first author, year of publication, location of the study, sampling size, study patient population, duration of patient follow-up, duration of EECF therapy, and adequate data on CCS.

Statistical Analysis

We used data from CCS class reported as the proportion of patients improving by at least 1 CCS angina class. Data were compared before and after EECF treatment. The impact of pooled proportion of EECF treatment was calculated using the Metaprop module in the R version 3.1.3 statistical software package. Proportion and 95%CI for outcome were separately calculated for each trial, and the proportion reported in each study was logit transformed prior to computing the pooled proportion.^{16,17} The selection of a Desimonian and Laird random-effect model versus Inverse of Variance fixed-effect model in the meta-analysis remains controversial. Tests of heterogeneity were applied to decide which method would be used to pool the results. Statistical heterogeneity was performed by I^2 statistic (the percentage of total variation across studies that is due to heterogeneity rather than chance) and the Q statistic. When the I^2 statistic was less than 50% and the P -value for the test of heterogeneity was ≥ 0.10 , we used a fixed-effect model to compute the pooled total proportion, whereas the heterogeneity was considered statistical significance, and a random-effect model was addressed to compute the pooled total proportion.¹⁸

When heterogeneity was present, subgroup analyses were performed to explore potential reasons based on baseline CCS class and age at enrollment. In addition, to inspect differences in EECF therapy among differing patient demographic, we analyzed the studies that had at least 60% of patients having previously undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) or having a previous myocardial infarction (MI). Moreover, the studies that had at least 30% of patients having diabetes mellitus (DM) were analyzed as well.

Sensitivity analysis was carried out to evaluate the influence of individual trials on the overall pooled results. Moreover, we excluded the studies that had large sample size to verify the robustness of the pooled proportion. To evaluate potential publication bias, funnel plots and the Begg rank correlation test and Egger linear regression test were used. P -value less than 0.10 level was considered significance.¹⁹

RESULTS

Search Results

We initially identified 762 potentially relevant articles. Seventy-one articles were considered to be of eligibility and were retrieved for full-text review. Fifty-three articles were excluded, and finally 18 studies^{20–37} reporting data on CCS class were included in our meta-analysis. A flow diagram of study selection is presented (Fig. 1).

Characteristics of Included Studies

Baseline characteristics of the 18 studies with a total 1768 patients in this meta-analysis are shown in Table 1. The follow-up period varied from 1 to 42 months. The patient population were male predominately, and baseline CCS were I–IV, II–IV, and III–IV correspond to the 4,^{20,21,33,34} 8,^{24–26,28,29,32,35,37} and 3 studies,^{23,30,31} respectively. The remaining studies on CCS were not reported.

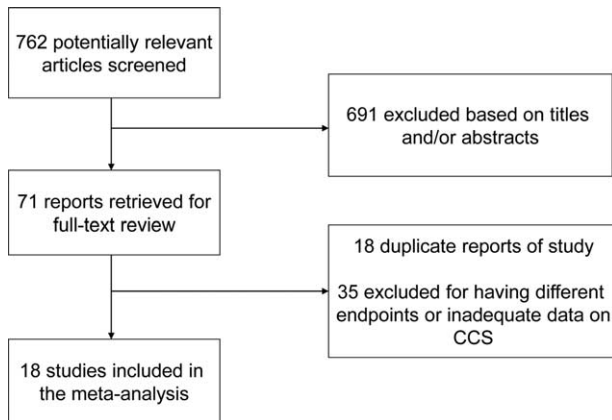


FIGURE 1. Flow diagram of study selection for meta-analysis.

Outcome Analysis

Our results suggested that angina class improved by at least 1 CCS class in 85% of patients from before to after EECP treatment (95% confidence interval [CI] 0.81–0.88, $I^2 = 58.5%$, $P < 0.001$) (Fig. 2). The degree of benefit in studies enrolling patients with baseline CCS classes I–IV, II–IV, and III–IV were 87% (95%CI 0.82–0.90), 82% (95%CI 0.77–0.86), and 88% (95%CI 0.68–0.96), respectively (Table 2). The results of subgroup analysis by at least 60% enrollment patients were also shown in Table 2.

Sensitivity analysis was conducted to inspect the potential sources of heterogeneity. Exclusion of any single study did not remarkable alter the overall pooled proportion, with a range from 84% (95%CI 0.81–0.87, $I^2 = 30.6%$) to 86% (95%CI 0.82–0.89, $I^2 = 56.5%$) (Fig. 3). We excluded 3 large studies^{20,21,36} to compute the overall pooled proportion with a fixed effect model, the pooled proportion was 82% (95%CI 0.79–0.86, $I^2 = 18%$, $P = 0.2528$) (Fig. 4).

Publication Bias

To evaluate potential publication bias, funnel plot was drawn, and Begg rank correlation test as well as Egger linear regression test was conducted. Funnel plot (Fig. 5) showed some asymmetry, but the Begg rank correlation test and Egger linear regression test showed no publication bias ($P = 0.1495$ and 0.2859, respectively).

DISCUSSION

The EECP therapy has been studied for almost a half century now. It is considered as a valuable, safe, and low-cost outpatient treatment for refractory angina. The technique of EECP consists of 3 pairs of pneumatic cuffs that were wrapped around the lower extremities, lower and upper thighs, and buttocks. The cuffs are inflated sequentially, applying 250 to 300 mmHg of external pressure during early of diastole, producing an improvement in coronary perfusion and thus increasing both venous return³⁸ and cardiac output.³⁹ On the onset of systole, the cuffs are then deflated reducing peripheral resistance and left ventricular afterload. A typically treatment sessions are 1 hour daily over 7 weeks for a total treatment course of 35 hours. A finger plethysmogram and electrocardiograph are utilized to monitor parameters.

Previous publication of EECP therapy on CCS class showed that 86% of 949 patients improved by at least 1 CCS functional class.⁴⁰ In our meta-analysis, 85% of the patients undergoing EECP treatment had a reduction by at least 1 CCS class. The result was consistent with another report from an EECP consortium.⁴¹ In that study, an improvement was found in 74% of 2289 patients who were in CCS angina classes III–IV at baseline by one functional class. Nearly 40% of the patients in class III and IV improved 2 or more classes. It was to our interest that both men and women responded to the EECP treatment equally. It indicated that this treatment could be generalized to include women and advanced those who had chronic refractory angina. Because this population group were at increased complications and many had less durable results with CABG or angioplasty. The age may influence the effectiveness of patients to EECP treatment, so subgroup analysis based on age was performed in our meta-analysis. Compared with the elder group (≥ 65 years), patients younger than 65 years did not show a significant improvement on CCS class post-EECP (84 vs 87%). However, there was a trend that the younger benefited the most. One study⁴¹ suggested that the group of patients younger than 57 years derived greater likelihood of improvement from EECP. Indeed, elderly patients may have comorbid diseases, including DM, hypertension, and chronic heart failure (CHF), which decrease the ability to recruit and/or develop collaterals. Moreover, the possible explanations and conclusions need further studies to verify. Previous studies^{28,33,37} showed that about more than 70% of the patients retained improvement in CCS after 1-year follow-up. Erdling et al³² and Michaels et al.⁷ reported a reduction by ≥ 1 angina class that sustained at 2 years. The later study suggested that 50% had an improvement in the quality-of-life post-EECP that was also lasted at 2 years. Besides the prior publication³⁶ that the patients were followed up for 3.5 years indicated that about 66.4% sustained EECP treatment benefit. Even so, further studies were warranted to assess the long-term effects of EECP therapy.

Which group of patients did obtain utmost benefit from EECP treatment? Our results indicated that a greater degree of benefit in those having a higher baseline CCS class. In the International EECP Patient Registry (IEPR) examined the benefit and safety of EECP therapy in 978 patients with no exclusion criteria performed, approximately 85% of the patients treated were in CCS class III–IV with no candidate for further invasive revascularization and 81% of patients had a reduction by at least 1 CCS immediately after treatment with lower adverse effect.⁴² Lawson et al⁴³ studied 112 patients with CCS II angina versus 1346 patients with class III–IV angina using data from IEPR. Compared with 78% of patients in CCS III–IV who had at least 1 CCS class improved post-treatment, the patients in class II was 61% ($P < 0.01$). At 2 years follow-up, MACE or repeat EECP treatment remained significantly, 70 versus 81%, respectively ($P < 0.05$). Although the greatest improvement was obtained in the patients most severely disabled at 2 years post-EECP, the patients who had mild angina benefited from EECP as well. The IEPR data were also used to examine the effect of EECP in 548 patients with a history of CHF.⁴⁴ The heart failure cohort was older, with more females, a greater duration of CAD, more prior infarcts and revascularization. Compared with the cohort without a history of CHF, patients in the CHF cohort with CHF maintained their reduction in angina, but they were significantly more likely to have experienced an MACE end point at 6 months follow-up. In prior publication, EECP has increased maximal oxygen up-take and exercise tolerance in patients with CHF.⁴⁵ Linnemeier

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

First Author	Publication Year	FU, months	Patients, No*	Mean Age, years	Male, %	Baseline CCS	Duration of EECP, weeks	Previous MI, %	Previous PCI, %	Previous CABG, %	Previous DM, %	No. of Patients With CCS ≥ 1 Improvement, n (%)
Stys ²⁰	2001	NA	395	66.1	80	I-IV	35/7	NA	NA	NA	NA	349(88)
Stys ²¹	2002	NA	175	61	89	I-IV	35/7	51	75	41	21	149(85)
Shechter ²²	2003	1	23	66	96	NA	35/7	74	74	91	39	17(74)
Bonetti ²³	2003	NA	20	68	75	III-IV	35	70	60	50	35	20(100)
Tartaglia ²⁴	2003	NA	25	68	92	II-IV	35/7	NA	32	64	20	24(96)
Henrikson ²⁵	2004	NA	28	62	79	II-IV	35/7	79	61	68	46	23(82)
Michaels ²⁶	2005	1	34	61	81	II-IV	35/7	70	54	66	49	27(79)
Nichols ²⁷	2006	NA	20	62	80	NA	35/7	30	60	70	35	20(100)
Loh ²⁸	2006	12	58	66	89	II-IV	35/4-7	71	20	80	16	50(86)
Novo ²⁹	2006	6	25	65	96	II-IV	35	64	64	68	36	21(84)
El-Sakka ³⁰	2007	NA	44	NA	100	III-IV	35/7	NA	NA	NA	NA	34(77)
Michaels ³¹	2007	1	24	62	71	III-IV	35	63	88	63	44	22(92)
Erdling ³²	2008	24	78	66	81	II-IV	35	60	58	73	21	62(79)
Soran ³³	2012	12	78	61.3	76	I-IV	35	70	NA	NA	32	71(91)
Wu ³⁴	2012	6	34	66	91	I-IV	35/7-8	56	76	62	32	26(76)
Bozorgi ³⁵	2013	6	20	61.5	95	II-IV	35/7	NA	15	65	25	15(75)
Gandhi ³⁶	2014	42	637	60.7	82	NA	35/7	39	11	7	47	586(92)
May ³⁷	2015	12	50	62.5	72	II-IV	35/7	58	58	8	24	41(82)

CABG = coronary artery bypass graft, CCS = Canadian Cardiovascular Society, DM = diabetes mellitus, EECP = enhanced external counterpulsation, FU = follow-up, MI = myocardium infarction, NA = not available, PCI = percutaneous coronary intervention.

* No. of patients those who completed the course of EECP treatment.

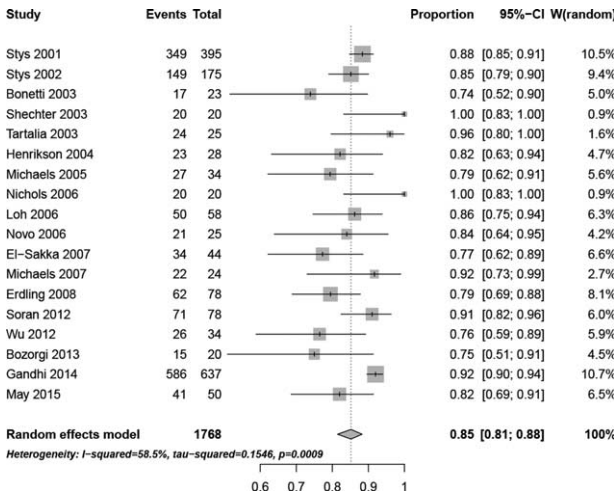


FIGURE 2. Forest plot of the overall pooled proportion and 95% confidence interval from 18 studies.

et al⁴⁶ reported effect of EECP in patients with DM. Despite a high-risk profile among the DM group than nondiabetes (ND), post-EECP angina reduction was reported on the CCS class in the majority of patients (DM vs ND, 69 vs 72%, *P*=NS). Quality of life was significantly improved and 1-year mortality was similar to coronary intervention.

To the best of our knowledge, no head-to-head prospective, randomized, controlled studies have been performed to compare the effect of elective invasive produces with EECP treatment on CCS class. One study compared patients enrolled

in the IEPR with National Heart, Lung, and Blood Institute Dynamic Registry of patients who underwent elective PCI. After 1-year follow-up, the survival rate was similar in both cohorts.⁴⁷ The data were come from 2 registries enrolling at primarily different centers, so presence of the potential bias was inevitable. In another report, 4454 of patients with prior PCI and/or CABG compared with 215 of patients who were suitable for PCI and/or CABG, but chose EECP as their initial revascularization treatment.⁴⁸ After EECP treatment, improvements in CCS, anginal episodes, and nitroglycerin use were seen in 2 cohorts, which sustained 6 months.

The mechanism underlying the benefit of EECP-derived is under investigation. The possible mechanisms include improvement in endothelial function, development of collateralization, regression of atherosclerosis, and peripheral “training effects” similar to exercise.⁶ The acute hemodynamic effect produced shear stress which could lead to increased endothelial cell production of nitric oxide (NO) and prostacyclin, powerful factors of vasodilatation. The studies reported that the level of NO increased, brain natriuretic peptide and serum endothelin-1 concentration reduced after EECP treatment.^{12,49} Sessa et al⁵⁰ found that chronic exercise promotes NO synthesis gene expression and coronary NO production in dog model. This process was initiated post-EECP with improved their exercise tolerance. Masuda et al¹² showed an improvement in both resting and post-exercise perfusion. This may indirectly promote by opening preexist collaterals or developing new ones via increased transmural pressure gradients during EECP.^{51,52}

LIMITATIONS

Firstly, the aim of this meta-analysis was to assess the effect of immediately after EECP treatment. Therefore, the

TABLE 2. Subgroup Analysis

Subgroup	No. of Studies	Patients, No.	Effect Size	95% CI	I ² , %	Q	P
Age, years							
<65 patients	9	1066	0.87	0.81–0.91	61.2	20.60	0.0083
≥65 patients	8	658	0.84	0.78–0.89	46.9	13.17	0.0068
Baseline CCS							
I–IV	4	682	0.87	0.82–0.90	45.1	5.47	0.1407
II–IV	8	318	0.82	0.77–0.86	0	4.55	0.7149
III–IV	3	88	0.88	0.68–0.96	54.8	4.42	0.1095
NA	3	680	0.89	0.70–0.96	77.5	8.88	0.0118
Previous CABG							
<60% Patients	4	882	0.88	0.81–0.93	74.5	11.75	0.0083
≥60% Patients	11	369	0.81	0.77–0.85	0	9.97	0.4433
Previous MI							
<60% Patients	5	916	0.87	0.78–0.92	76.8	17.21	0.0018
≥60% Patients	9	368	0.84	0.79–0.88	15.5	9.47	0.3041
Previous PCI							
<60% patients	7	902	0.85	0.77–0.91	74	23.05	0.0011
≥60% patients	8	349	0.84	0.78–0.88	17.1	8.44	0.2951
Previous DM							
<30% Patients	6	406	0.83	0.79–0.87	0	4.99	0.4177
≥30% Patients	10	923	0.87	0.80–0.91	62.1	23.76	0.0047
CHF	8	432	0.84	0.81–0.88	32.7	10.40	0.1668

CABG = coronary artery bypass graft, CCS = Canadian Cardiovascular Society, CHF = chronic heart failure, CI = confidence interval, DM = diabetes mellitus, I², Q = heterogeneity test, MI = myocardial infarction, NA = not available, PCI = percutaneous coronary intervention.

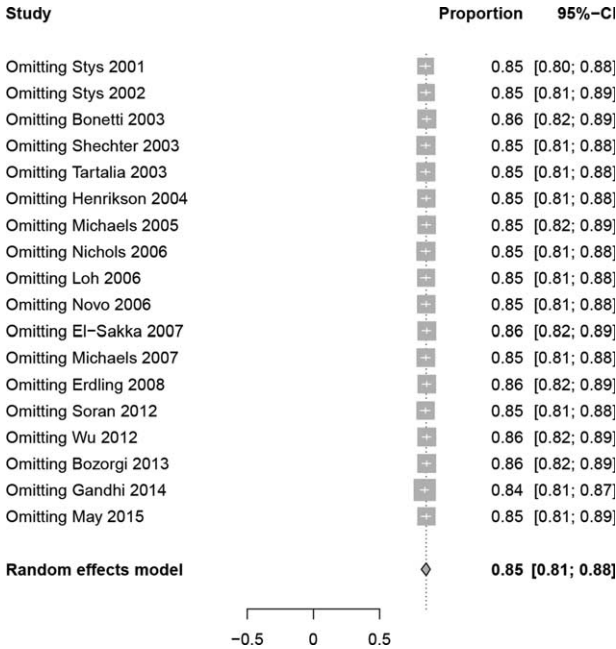


FIGURE 3. Sensitivity analysis of the efficacy of EECp therapy on CCS. CCS=Canadian Cardiovascular Society, EECp=enhanced external counterpulsation.

long-term maintenance of improved on CCS needs further investigation. Secondly, because the nature of EECp procedure makes performing a randomized, controlled, blinded trial difficult. We enrolled studies with the feature of prospective, nonrandomized-controlled. The first and an only multicenter, prospective, randomized, blinded placebo (sham) controlled trial was conducted in MUST-EECP.¹³ In addition, EECp, as a new treatment for refractory angina, attracted patients more enthusiasm, so the device placebo effect cannot be excluded. In generally, more further randomized controlled trails are necessary to assess the impact of EECp for the treatment of patients with chronic CAD.

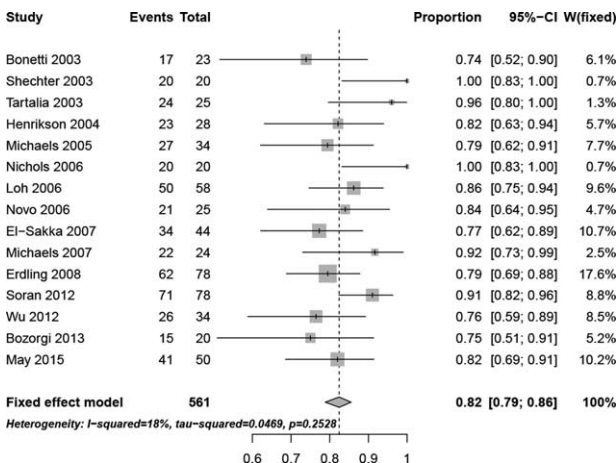


FIGURE 4. The meta-analysis of exclusion three large studies.

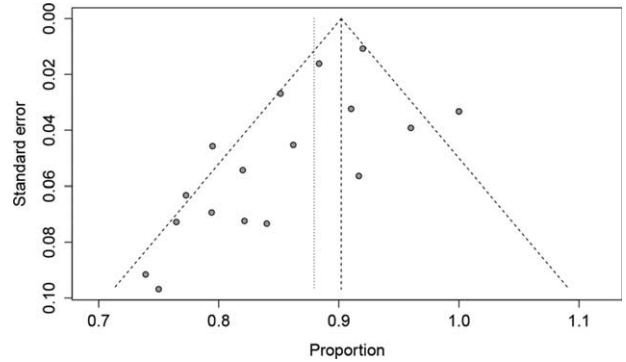


FIGURE 5. Funnel plot applied to evaluate publication bias.

CONCLUSIONS

Our meta-analysis suggested that 85% of the patients those underwent EECp therapy improved by at least 1 CCS class immediately post-EECP treatment. The CCS angina class is a relatively minor predictor of prognosis and freedom from events, so our results are noteworthy and the studies evaluated long-term benefit of EECp therapy are warranted. Currently, EECp treatment provides a safe, well-tolerated, valuable option for patients who were unresponsive to maximal medical management and/or invasive therapy. Of note, in combination with other antianginal drugs, the FDA approved Ranolazine to treatment for chronic angina in 2002.

ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (No. 81270175, No.81470404) and the Natural Science Foundation of Shandong Province, China (No.ZR2014HM107) for the support.

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