

ORIGINAL PAPER

Effect of enhanced external counterpulsation on medically refractory angina patients with erectile dysfunction

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SUMMARY

Patients with refractory angina often suffer from erectile dysfunction. Enhanced external counterpulsation (EECP) decreases symptoms of angina, and increases nitric oxide release. This study evaluated the effect of EECP on sexual function in men with severe angina. The International Index of Erectile Function (IIEF) was used to assess erectile function of severe angina patients enrolled in the International EECP Patient Registry. Their symptom status, medication use, adverse clinical events and quality of life were also recorded before and after completing a course of EECP. A cohort of 120 men (mean age 65.0 ± 9.7) was enrolled. The men had severe coronary disease with 69% having a prior myocardial infarction, 90% prior coronary artery bypass graft or percutaneous coronary intervention, 49% with three vessel coronary artery disease, 86% were not candidates for further revascularisation, 71% hypertensive, 83% dyslipidaemia, 42% diabetes mellitus, 75% smoking and 68% using nitrates. Functional status was low with a mean Duke Activity Status Inventory score of 16.6 ± 14.8 . After 35 h of EECP anginal status improved in 89%, and functional status in 63%. A comparison of the IIEF scores pre- and post-EECP therapy demonstrated a significant improvement in erectile function from 10.0 ± 1.0 to 11.8 ± 1.0 ($p = 0.003$), intercourse satisfaction (4.2 ± 0.5 to 5.0 ± 0.5 , $p = 0.009$) and overall satisfaction (4.7 ± 0.3 to 5.3 ± 0.3 , $p = 0.001$). However, there were no significant changes in orgasmic function (4.2 ± 0.4 to 4.6 ± 0.4 , $p = 0.19$) or sexual desire (5.3 ± 0.2 to 5.5 ± 0.2). The findings suggest that EECP therapy is associated with improvement in erectile function in men with refractory angina.

Introduction

Enhanced external counterpulsation (EECP) is a non-invasive treatment used for patients with angina refractory to medical therapy who are poor revascularisation candidates. The system consists of three sets of cuffs wrapped around the calves, lower and upper thighs of the patient. The pneumatic cuffs are sequentially inflated at the onset of diastole; providing diastolic augmentation, increasing venous return, cardiac output and coronary blood flow. Cuff deflation occurs at the end of diastole, providing left ventricular unloading and further increasing cardiac output. EECP is commercially available in the United States, Europe and Asia. The Food and Drug Administration has cleared EECP devices for use in unstable and stable angina pectoris, acute myocardial infarction

(MI), congestive heart failure and cardiogenic shock. It was approved for coverage by the Centers for Medicare and Medicaid Services for patients who have been diagnosed with disabling angina with Canadian Cardiovascular Society (CCS) classification class III or class IV.

Enhanced external counterpulsation has acute haemodynamic effects on the systemic circulation that include a reported 88% increase in infrarenal abdominal aortic blood flow and a 144% increase in internal iliac flow (1). EECP therapy is also associated with progressive increase in nitric oxide levels that persist beyond the immediate course of therapy (2) and are associated with decreased systemic resistance (3) and normalisation of endothelial function as assessed by reactive hyperaemia-peripheral artery tonometry (4,5). By increasing nitric oxide

What's known

Patients with refractory angina often suffer from erectile dysfunction (ED). There is considerable literature documenting the benefit of phosphodiesterase inhibitors such as Viagra and Cialis in improving erectile function. However, there is considerable risk in taking phosphodiesterase inhibitors for patients with coronary artery disease who are also using nitrates for their angina.

What's new

This report suggests that an external mechanical (EECP) therapy can be effective in improving erectile function in a cohort of coronary disease patients with refractory angina and significant comorbidity (i.e. peripheral vascular disease and diabetes mellitus). The improvement also supports the working mechanism of action for EECP; that local mechanical therapy can have systemic effects, mediated by increases in nitric oxide and improved endothelial function.

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production, EECP potentially augments penile arterial vasodilation and may enhance erections (6). Potential cardiac mechanisms contributing to the benefits of EECP therapy include relief of exertional angina, improvement of cardiac output and reserve, decrease in myocardial ischaemic burden. The improvement in physical health demonstrated with EECP, such as a decrease in angina class and improved exercise tolerance, has also been shown to benefit psychosocial functioning with a third of patients reporting improved sexual activity in an earlier small study (7).

A small study of 13 patients with a primary diagnosis of erectile dysfunction (ED) treated with EECP demonstrated dramatic improvement in the signs and symptoms of ED with therapy. After completing the 20-h course of treatment with EECP there was an 88% increase in penile artery peak systolic flow, and an improvement in erectile function (1.5–2.3 on a scale of 0–3). Post-EECP 84% of the patients demonstrated improvement in ED, with 40% having complete resolution (6).

However, whether the cardiac patients with refractory angina will realise similar benefits is uncertain, particularly given the high diabetic comorbidity and chronic need for medications such as beta blockers, antihypertensives and diuretics impacting on ED. To investigate the effect of EECP on sexual function in men with severe medically refractory angina a sub-study, code named Mens Health, was performed using patients enrolled in the International Enhanced External Counterpulsation Patient Registry 2 (IEPR 2).

Methods

The IEPR 2 is co-ordinated at the Graduate School of Public Health at the University of Pittsburgh, enrolling consecutive patients treated with EECP from 73 participating centres, typically with severe, medically refractory angina. All sites had approval of the Institutional Review Board and patients gave their written informed consent. Data prior to EECP treatment included information on patient demographics, medical and cardiovascular history, angina status, quality of life, medications and Duke Activity Status Inventory (DASI) scores. All male patients enrolling in the IEPR from 16 participating sites were asked if they would like to participate in this study. The 15-item, self-administered questionnaire of the International Index of Erectile Function (IIEF) (8) was used to assess ED before and after completing a course of EECP. A repeat IIEF was completed within the month following completion of EECP therapy. The IIEF identifies five domains (erectile function, orgasmic function, sexual desire, intercourse satisfac-

tion and overall satisfaction) associated with male sexual function. A higher score on each domain represents better functioning. The completed IIEF forms were submitted directly to the University of Pittsburgh in an anonymous manner. The completed forms were never seen by the clinical centres, and were matched to the clinical data by means of a unique code. EECP treatment course was typically prescribed for 1 h/day, 5 days/week for a total of 35 h. Patients were included in the study if they had one or more hours of treatment. The treatment course could be altered by patient preference, clinical course or response to therapy.

Post-treatment, all patients in the Registry were reassessed for symptom status, medication use, adverse clinical events, additional interventions and quality of life. Major adverse cardiovascular events (MACE) during treatment were identified, namely: all-cause mortality, non-fatal MI and revascularisation with angioplasty or bypass surgery. Data from the Mens Health Study were analysed for each domain of the IIEF before and after therapy. A comparison of the clinical baseline characteristics of men participating in the study was made with all men not participating.

Statistical analysis

Discrete variables were analysed by chi-squared testing and continuous variables by paired or unpaired *t*-test as appropriate. Significance was defined as $p < 0.05$.

Results

One hundred and twenty men completed the IIEF forms pre- and post-EECP. A comparison group of 644 men who were in the IEPR 2 registry but did not participate in the Mens Health study was used as a comparison in evaluating their angina status. Baseline demographics demonstrated the Mens Health subgroup to have largely similar characteristics to the overall group of men not enrolled in the substudy.

Entry characteristics

The mean age of the Mens Health cohort of patients was 65.0 ± 9.7 years with an average duration of clinical coronary artery disease (CAD) of 10.7 ± 8.9 years. Medical history was comparable with that of overall men in the IEPR 2 with 69% having had a prior MI, 90% having had prior revascularisation, 70% with percutaneous coronary intervention (PCI) and 67% with previous coronary artery bypass graft (CABG). Triple-vessel CAD was present in 49%, two-vessel coronary disease in 23%

and 22% had single-vessel disease; only 14% were considered candidates for further revascularisation. The mean left ventricular ejection fraction (LVEF) was $49 \pm 12\%$; and 13% of the patients had an LVEF of $< 35\%$. The prevalence of cardiovascular risk factors was expectedly high, including: 71% with a family history of premature atherosclerotic cardiovascular disease, 68% with hypertension, 83% with hyperlipidaemia, 42% with diabetes mellitus (DM), 75% with a history of smoking (7% current smoking). Severe disabling angina with CCS class III and IV was present in 93% of patients with an average of 9.2 ± 15.1 anginal episodes/week and nitroglycerine (NTG) used on an average of 8.0 ± 13.3 times/week. Medications included: 79% took beta blockers, 40% diuretics, 58% angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), 38% calcium channel blockers, 68% nitrates, 84% lipid-lowering drugs and 76% antiplatelet agents. Compared with the non-participating men, the Mens Health cohort had a significantly greater proportion of patients with a history of transient ischaemic attacks but significantly lower proportion with hypertension, multivessel coronary disease and ischaemic cardiomyopathy (see Table 1). In the Mens Health group, 81% had moderate to severe limitation of activity because of cardiac limitations and 39.3% had previously consulted a physician for sexual problems. The majority of Mens Health patients (58.6%) never or almost never had spontaneous erections at night or on awakening. Medication to enhance sexual

performance had been used in 38.4% (Muse 5% (Alprostadil: Vivus, Mountain View, CA, USA), Aphrodyne 2% (Sildenafil: Pfizer, New York, NY, USA), Viagra 30% (Yohimbine: Star Pharmaceuticals, Ft Lauderdale, FL, USA) and others 3%). Long-acting nitrates were used in 68% of patients and Viagra in 30%; 16% reported using both nitrates and Viagra and 15% used both nitroglycerin spray or sublingual and Viagra.

EECP treatment course

The Mens Health cohort of patients received a mean EECP treatment course of 35.4 h with 91.7% completing the course as prescribed. This was a significantly greater number of hours of therapy and a higher completion rate than that of non-participating men in the IEPR 2 and was associated with a lower incidence of MACE (0.8% vs. 5.8%; $p < 0.05$). The only major adverse cardiovascular event occurring over the course of therapy was one MI (0.8%). No patients in the Mens Health group had a revascularisation procedure (PCI or CABG) during their EECP treatment. There were no significant changes in medical therapy over the course of EECP treatment.

CCS angina class and DAS1

Anginal status by the CCS classification improved in 89% of patients in the Mens Health cohort; this is $>78\%$ improvement noted in non-participating men in the IEPR 2, ($p < 0.01$). Post-EECP only 9% had CCS class III or IV angina. In the Mens Health

Table 1 Comparison of men participating and not participating in the Men's Health Study

	Mens health (N = 120)	IEPR 2 (N = 664)	Significance
Age	65.0 \pm 9.7	65.9 \pm 10.5	ns
Years since CAD diagnosis	10.7 \pm 8.9	11.6 \pm 9.1	ns
Prior MI	68.9%	70.5%	ns
Left ventricular EF	48.6 \pm 11.8	46.8 \pm 14.4	ns
Ischaemic CM	23.7%	38.3%	< 0.01
Multivessel CAD	71.6%	80.6%	< 0.05
Prior PCI/CABG	90.0%	91.0%	ns
PCI/CABG candidate	13.9%	14.9%	ns
PVD	19.8%	23.7%	ns
Family history of CAD	70.7%	79.2%	ns
Diabetes mellitus	41.9%	41.4%	ns
Hypertension	68.1%	77.4%	< 0.05
Hyperlipidaemia	83.1%	89.5%	ns
Past/present smoking	74.8%	74.7%	ns
TIA's	17.8%	10.0%	< 0.05

The values are expressed as mean \pm standard deviation or percentages. CAD, coronary artery disease; CABG, coronary artery bypass graft; CM, cardiomyopathy; EF, ejection fraction; IEPR 2, International Enhanced External Counterpulsation Patient Registry 2; MI, myocardial infarction; ns, not significant; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA's, transient ischaemic attacks.

Table 2 Effect of EECP on CCS angina class and DASI score in 120 angina patients with erectile dysfunction

	Pre-EECP	Post-EECP	p-value
No angina	0	22.2%	< 0.05
CCS class I	0	27.4%	
CCS class II	6.7%	41.0%	
CCS class III	77.5%	7.7%	
CCS class IV	15.8%	1.7%	
DASI score	16.6 ± 14.8	21.7 ± 14.5	< 0.05

The values are expressed as mean ± standard deviation or percentages. CCS, Canadian Cardiovascular Society; DASI, Duke Activity Status Inventory; EECP, enhanced external counterpulsation.

cohort, anginal episodes decreased from 9.2 ± 15.1 at baseline to 2.2 ± 4.3 episodes/week after EECP ($p < 0.01$), and NTG use decreased from 8.0 ± 13.3 to 3.6 ± 3.2 per week ($p < 0.01$). This is comparable with the overall men in IEPR 2 with decrease in angina episodes from 10.5 ± 14.7 to 3.3 ± 9.7 per week and NTG usage from 9.3 ± 13.4 to 5.9 ± 11.5 per week. The DASI score improved in 63%, with a baseline average score of 17 ± 15 pre-EECP treatment improving to an average of 22 ± 15 post-EECP treatment. These results are comparable with those of the overall IEPR 2 where 62% of men demonstrated improvement from an average pre-EECP DASI score of 14 ± 13 to a post-EECP score of 19 ± 14 (see Table 2).

International index of erectile function

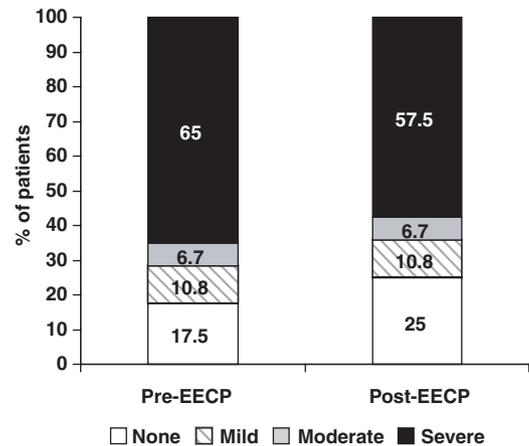
The IIEF showed an average score of 28 (out of a possible 75) at baseline with a mean score of 10.0 in the erectile function domain, consistent with ED. A comparison of the IIEF 15 pre- and post-EECP therapy demonstrated three domains with a significant improvement; erectile function, intercourse satisfaction and overall satisfaction. Orgasmic function and sexual desire were not significantly changed over the course of EECP therapy, as shown in Table 3.

Figure 1 shows the change in the severity of erectile dysfunction with treatment. There is an increase in the proportion of patients with no symptoms of ED and a concomitant decrease in the proportion with severe ED. Anti-anginal medication use affecting ED did not change significantly over the course of therapy, especially beta blockers (80% pre- and 73% post-EECP), calcium channel blockers (38% vs. 42%), and long-acting nitrates (68% at both time points; $p = ns$). The proportion of patients reporting spontaneous erections at night or upon awakening did not change significantly with EECP (41% pre to 47% post; $p = ns$).

Table 3 Effect of EECP on International Inventory of Erectile Function in 120 angina patients with erectile dysfunction

IIEF Domain	Pre-EECP	Post-EECP	p-value
Erectile function	10.0 ± 10.9	11.8 ± 11.6	0.0033
Orgasmic function	4.2 ± 4.3	4.6 ± 4.3	0.19
Sexual desire	5.3 ± 2.4	5.5 ± 2.3	0.20
Intercourse satisfaction	4.2 ± 5.2	5.0 ± 5.3	0.0092
Overall satisfaction	4.7 ± 2.9	5.2 ± 2.9	0.0011
Total score	28.2 ± 24.5	31.7 ± 24.5	0.010

The higher score indicates better functioning for each domain. The values are expressed as mean ± standard deviation. EECP, enhanced external counterpulsation; IIEF, International Index of Erectile Function.

**Figure 1** Severity of erectile dysfunction pre- and post-enhanced external counterpulsation (EECP) treatment

Discussion

Erectile dysfunction has multiple causes including vascular status, neurological function, psychological factors and comorbidity. Men with structural heart disease and medically refractory angina have a particularly high prevalence of ED because of cardiac dysfunction, exertional angina, psychological factors and comorbidity including a high prevalence of peripheral vascular disease and DM. They also have special challenges including a need for nitrates, beta blockers and blood pressure control medications, which may exacerbate the ED. A consensus panel of experts reviewed recent multinational studies in safety and drug interaction data for three phosphodiesterase type 5 inhibitors (sildenafil, tadalafil and vardenafil), with emphasis on the safety of these agents in men with ED and concomitant cardiovascular disease. ED is an early symptom of cardiovascular disease,

because of the common risk factors and pathophysiology mediated through endothelial dysfunction. Major comorbidities include diabetes, hypertension, hyperlipidaemia and heart disease. The recognition of ED as a warning sign of silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise. Men with ED and other cardiovascular risk factors (e.g. obesity, sedentary lifestyle) should be counselled in lifestyle modification (9). Therefore the surprise finding of this study is the fact that despite the need for nitrates for severe, refractory angina, many of the men in this study were willing to risk the use of Viagra, demonstrating the importance cardiac patients place on sexual function.

Enhanced external counterpulsation has been shown to improve many of the factors contributing to ED. There is evidence of treatment associated with acute improvement in visceral and penile artery blood flow, a dose and time-related increase in nitric oxide and endothelial function, increase in several vascular growth factors (vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF)) (10), an improvement in myocardial perfusion in areas of ischaemia (10,11), a decrease in the signs and symptoms of myocardial ischaemia, an improvement in the quality of life and psychosocial functioning. While it is difficult to separate out the improvement in general health and functioning post-EECP from other factors, the IIEF suggests improvement in the domains of erectile function, intercourse satisfaction and overall satisfaction with EECP and no significant change in orgasmic function or sexual desire. The former domains are more closely related to neurovascular health, while the latter domains are probably somewhat more closely related to libido. As there were improvements after EECP treatment in exercise capacity, cardiac status and overall general well-being, it is impossible to differentiate the mechanism of improvement in ED in terms of endothelial function vs. improvement in physical and psychological factors.

The findings of improvement in erectile function with EECP in cardiac patients with medically refractory angina are qualitatively similar to those reported for patients with a primary diagnosis of ED. However, as might be expected, the magnitude of benefit was less in the end-stage CAD patient. It is possible that improvements in exercise capacity after EECP and overall general well-being covaried with changes in sexual function and that this clustering is an overall favourable sign for long-term prognosis. However, long-term follow-up was not performed and the durability of the improvement in ED is unknown.

Further limitations of the study include the lack of a control group and the possibility of a confounding placebo effect.

Future research to assess and confirm the potential of EECP to restore a functional erectile mechanism via improvement in vascular status might include: nocturnal penile tumescence and rigidity (NTPR) as assessed by Rigiscan-NTPR and duplex ultrasound of the penile arteries to calculate peak systolic blood flow and resistance. Long-term follow-up and correlation of ED, NO levels, and cardiac, psychological, and physical functioning also merit further investigation, as does the effect of different EECP dose and interval treatment regimens (initial, maintenance and retreatment).

Conclusions

Patients enrolled in the Mens Health substudy were comparable with the general population of men enrolled in the IEPR 2, a study of the effect of EECP in patients with medically refractory angina. The studied population had multiple conditions associated with ED including: older age, advanced cardiovascular disease, a high prevalence of diabetes and hypertension, a need for drugs affecting sexual function, moderate to severe physical impairment and decreased psychosocial functioning. A high prevalence of ED was noted in these patients with improvement in the domains of erectile function, intercourse satisfaction and overall satisfaction after treatment with EECP. The findings suggest EECP remains effective in end-stage CAD patients in mediating an improvement in vascular function and in associated ED.

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