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The immediate and long-term outcome of enhanced external counterpulsation in treatment of chronic stable refractory angina

P. H. LOH[1], A. A. LOUIS[1], J. WINDRAM[1], A. S. RIGBY[1], J. COOK[1], S. HURREN[1], N. P. NIKOLAY[1], J. CAPLIN[2] & J. G. F. CLELAND[1,2]

From the [1]Academic Cardiology Department, University of Hull, Kingston-upon-Hull; and [2]Department of Cardiology, Hull and East Yorkshire NHS Hospitals Trust, Castle Hill Hospital, Kingston-upon-Hull; UK

Abstract. Loh PH, Louis AA, Windram J, Rigby AS, Cook J, Hurren S, Nikolay NP, Caplin J, Cleland JGF (University of Hull, Kingston-upon-Hull; and Department of Cardiology, Hull and East Yorkshire NHS Hospitals Trust, Castle Hill Hospital, Kingston-upon-Hull; UK). The immediate and long-term outcome of enhanced external counterpulsation in treatment of chronic stable refractory angina. *J Intern Med* 2006; **259**: 276–284.

Background. Treatment of angina recalcitrant to conventional pharmacological therapy and revascularization remains problematic. Safe, effective and affordable treatments with high patient acceptability are desirable. Enhanced external counterpulsation (EECP) may fulfil these criteria better than many other proposed interventions.

Objective. To examine the immediate and long-term effect of EECP in treatment of chronic stable refractory angina.

Design. Prospective observational study of consecutive patients treated with EECP and follow-up for 1 year.

Setting. Teaching hospital.

Main outcome measures. Canadian Cardiovascular Society (CCS) angina grading, weekly angina frequency and glyceryl trinitrate (GTN) use.

Results. Sixty-one patients were treated with EECP and 58 completed a course of treatment. Further analysis is confined to those who completed EECP. About 52% of patients suffered from CCS III and IV angina prior to EECP. Immediately post-EECP, angina improved by at least one CCS class in 86% and by two classes in 59%. At 1-year follow-up, sustained improvement in CCS was observed in 78% of the patients. The median weekly angina frequency and GTN use were significantly reduced immediately after EECP [7 (4–14) vs. 1 (0–4) episodes per week and 7 (2–16) vs. 0 (0–2) times per week respectively, $P < 0.0001$; data in median (interquartile range)]. The reduction was sustained at 1-year follow-up. In 48 patients, their mean exercise time improved significantly after EECP [301 ± 130 s vs. 379 ± 147 s, $P < 0.0001$]. Major adverse treatment-related events were rare.

Conclusion. This study shows that for patients who fail to respond to conventional measures, a high proportion gain symptomatic benefit from EECP.

Keywords: angina pectoris, coronary artery disease, coronary heart disease, external counterpulsation, ischaemic heart disease, refractory pain.

Introduction

Some patients with angina pectoris have an inadequate response to pharmacological therapy and are either unsuitable for revascularization or have a risk/benefit ratio for revascularization that is unattractive. It is estimated that 250 000 patients will be affected each year in the developed countries [1, 2]. The European Society of Cardiology Joint Study Group on the treatment of refractory angina has highlighted the lack of evidence for many currently available treatment options [1].

Enhanced external counterpulsation (EECP) has emerged as one potential treatment for chronic refractory angina. EECP is a non-invasive outpatient-based treatment consisting of ECG-triggered, sequential compression of the lower limbs and buttocks using three pairs of pneumatic cuffs. The cuffs inflate in diastole, augmenting diastolic aortic pressure, and deflate before the onset of systole reducing systolic pressure. This reduces aortic impedance, increases mean coronary perfusion pressure and flow and may have effects on renal and peripheral vascular function and the endothelium. It has been proposed that these actions may improve coronary microvascular function and/or macroscopic collateral arterial supply [3–5].

A typical course of EECP involves 35 daily 1-h treatment sessions over 7 weeks. It is widely available in America and China but experience in Europe is limited. The aim of this study is to examine the safety and effectiveness of EECP on angina control and exercise performance in patients suffering from stable refractory angina pectoris. This prospective observational study is the largest cohort of patients reported from any European centre.

Methods

Design and patients

The study was conducted at Hull Royal Infirmary, a teaching hospital for Hull and York Medical School, UK. Patients were referred locally or from other centres throughout the country. For the purpose of this study, consecutive patients who received EECP treatment between February 2000 and July 2003 were prospectively followed for 1 year. These patients were referred for EECP treatment due to refractory stable angina pectoris despite pharmacological therapy and were considered to be unsuitable for or unwilling to consider revascularization by conventional percutaneous or surgical means. All patients had documented coronary artery disease (coronary angiography or history of myocardial infarction, MI) and evidence of ischaemia on exercise treadmill test and/or radionuclide imaging. Patients were excluded from EECP treatment according to established criteria, including aortic aneurysm or aortic regurgitation [6, 7]. Patients with prior EECP treatment were also excluded. The study complied with the Declaration of Helsinki and was approved by Hull and East Riding Local Research Ethics Committee and hospital Research and Development Board. Informed written consent was obtained from every patients.

All patients were assessed by a medical doctor prior to EECP. The relevant background medical history was recorded. An echocardiogram was performed to assess left ventricular function and exclude significant aortic regurgitation. An abdominal ultrasound was done to exclude clinically significant abdominal aortic aneurysm. The Canadian Cardiovascular Society (CCS) angina grading, angina frequency and use of short-acting glyceryl trinitrate (GTN) in the weeks prior to EECP, immediately after EECP and at 1-year follow-up were recorded. Exercise capacity was evaluated by comparing the second of two treadmill tests prior to EECP with tests conducted 2 weeks and 3–6 months post-EECP, using a Bruce or Modified Bruce protocol. The same protocol was used for each individual patient during each test. All minor events including skin blisters, bruises, leg discomfort, aggravated back or joint pain and increase in abdominal hernias that occurred during treatment period were recorded. All major events, including death, MI, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft operation (CABG), decompensated heart failure, new dysrhythmias and repeat EECP, and hospitalization due to a cardiac cause during treatment period and follow-up were also recorded.

EECP treatment

The EECP equipment (Model MC2 and TS3; Vasomedical Inc., Westbury, NY, USA) and treatment procedures have been described elsewhere [6, 7]. All patients received at least 35 1-h sessions of treatment over 4–7 weeks. For patients' convenience, after the initial five once-daily sessions, they were given a choice to increase their treatment to two sessions per day. Those who received two treatment sessions per day had at least 30 min in between the sessions. The cuff pressure applied was between 260 and 300 mmHg. The mean peak diastolic augmentation achieved was 1.6 (0.5), that is the diastolic arterial pressure exceeded systolic pressure by 60%. This is within the recommended range of 1.5–2.5 [6].

Statistical analysis

Descriptive data are presented as mean and standard deviations (SDs) or medians and interquartile range depending whether the data had a normal distribution or not. Binary and categorical data are presented as percentages. Changes in paired measurements were either analysed by McNemar's test (binary data) or the paired *t*-test (continuous data with a normal distribution) or Wilcoxon's test (non-normal data). The relationship between the baseline characteristics (Table 1) and the data at 1-year follow-up was explored by multiple logistic regression analysis with the main outcome measure change in CCS class. A forward stepwise procedure was adopted in which each baseline variable was entered in turn using a nominal level of 5% statistical significance. The variable with the lowest deviance was retained in the model and the whole process repeated until no more significant variables remained. From the logistic model odds ratios (ORs) and 95% confidence intervals (CIs) were generated. The OR is an approximation to the relative risk [8]. The SPSS (version 10; SPSS Inc., Chicago, IL, USA) and GLIM4 (The Numerical Algorithms Group Ltd, Oxford, UK) statistical computer packages were used to analyse the data. A nominal level of 5% statistical significance (two-tailed) was assumed throughout.

Table 1 Baseline characteristics ($n = 61$)

Age (years)	66 (6)
Age >65 years	56
Male	89
LVEF (%)	48 (15)
LVEF <35%	15
Medical history	
Duration of CAD (years)	14 (6)
Prior myocardial infarction	71
Prior PCI	20
Prior CABG	80
Prior PCI or CABG	84
More than 1 prior revascularization	31
Unsuitable for revascularization	84
Heart failure	23
Noncardiac vascular disease	23
Atrial fibrillation	10
Permanent pacemaker	7
Cardiovascular risk factors	
Diabetes mellitus	16
Hypertension	36
Hypercholesterolaemia	69
Family history of CAD	75
Smoker	
Previous	71
Current	3
Vessel disease	
Single	3
Double	12
Triple	85

All data are percentages unless otherwise stated as mean (SD). CAD, coronary artery disease; CABG, coronary artery bypass graft operation; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Results

Of 61 patients treated with EECP, three patients (5%) did not complete the treatment. Two had treatment discontinued because their pacemakers interfered with the triggering mechanism of EECP equipment, whilst a third suffered from an MI after 20 treatment sessions. These patients were excluded from analyses of treatment effect. At 1-year follow-up, four patients had died, 26 patients attended our department for a review whilst data were obtained by telephone in 28 patients.

Baseline characteristics

Table 1 describes the baseline characteristics of the patients. Over half of them were older than 65 years and majority were men. They had long history of coronary artery disease and most had an MI but the left ventricular ejection fraction (LVEF) remained preserved. The majority of them suffered from multivessel coronary disease with at least a prior revascularization and, in the opinion of their attending cardiologists or cardiothoracic surgeons, were not candidates for further conventional revascularization therapy. Three patients were considering the option of surgical revascularization whilst seven patients declined further attempts at revascularization after being advised of likely risk and benefit.

CCS angina class

Thirty-two patients had CCS III/IV angina at baseline (Table 2). Immediately after EECP angina severity was improved by at least one CCS class in 50 patients and by at least two classes in 34 of them (59%). These benefits were maintained at 1 year with 42 patients were at least one CCS class better than at baseline (Fig. 1). Of 32 patients with CCS III/IV angina at baseline, two (6%) reported no improvement, whilst 10 (31%) improved by one

Table 2 Angina class, weekly angina frequency, weekly on-demand glyceryl trinitrate (GTN) use and medications at pre-enhanced external counterpulsation (EECP), post-EECP and 1-year follow-up

	Pre-EECP	Post-EECP	1 year
No. of patients	61	58	54
Angina characteristics			
No angina*	0	36	26
CCS class*			
I	0	26	30
II	48	31	30
III	36	7	15
IV	16	0	0
Angina decreased ≥1 class		86	78
Median weekly angina (episodes week^{-1})	7 (2–16)	1 (0–4)†	2 (0–8)†
Patients reported reduction in angina		97	82
Patients reported >50% reduction in angina		85	78
Median weekly GTN use (times week^{-1})	7 (2–16)	0 (0–2)†	1 (0–11)‡
Patients reported reduction in GTN use		81	70
Patients reported >50% reduction in GTN use		76	69
Patients required on-demand GTN	85	47†	49†
Medications			
Aspirin	82	83	82
Antiplatelets	93	95	94
Antiplatelets/warfarin	98	98	98
Beta-blockers	75	81	82
Lipid-lowering agents	84	86	89
Long-acting nitrates	80	79	66§
Calcium channel blockers	66	67	52§
Nicorandil	56	55	48
Angiotensin-converting enzyme inhibitors	33	29	37
Diuretics	25	22	24

All data are percentages unless otherwise stated as median (interquartile range). *$P = 0.001$; †$P < 0.0001$ testing against pre-EECP; ‡$P < 0.0005$ testing against pre-EECP; §$P < 0.05$ testing against pre-EECP.

CCS class, 20 (63%) improved by at least two classes and seven (22%) became angina free.

As cardiac events and/or procedures could lead to a reduction in angina, we investigated the effects of EECP in the 42 (72%) patients who did not suffer from any cardiac event at 1-year follow-up. Twenty-one (50%) of these patients had CCS III/IV angina at baseline. Angina severity was improved by at least one CCS class in 38 (91%) patients and by at least two classes in 29 (70%) immediately post-EECP. At 1-year follow-up, angina severity was at least one CCS class better than pre-EECP in 34 (81%) patients, whilst 10 (24%) patients were still free of angina.

Of eight (14%) patients who did not improve their CCS class immediately post-EECP, all reported reduction in angina frequency and GTN requirement. At 1-year follow-up, one of these patients had died. CCS class improved in two patients and was stable in the remaining five. The angina frequency and sublingual GTN requirement were still improved in these five patients.

Reported weekly angina frequency

Immediately post-EECP, the reported weekly angina frequency was reduced in 56 patients (97%) from a median of 7 (4–14) to 1 (0–4) episodes per week ($P < 0.0001$). This represents a median reduction of 6 (3–14) episodes per week. At 1-year follow-up, the median weekly angina frequency was 2 (0–8) episodes per week and this remained lower than pre-EECP angina frequency ($P < 0.0001$; Table 2 and Fig. 2b). Forty-four patients (82%) were still experiencing less angina episodes at 1-year follow-up compared with pre-EECP and 26 of them (50%) had similar short- and long-term gain. A similar pattern was observed in the 42 patients who did not suffer any cardiac event at 1-year follow-up.

Weekly on-demand GTN use

At baseline, 51 patients (85%) required on-demand GTN for angina relief. This was reduced to 27

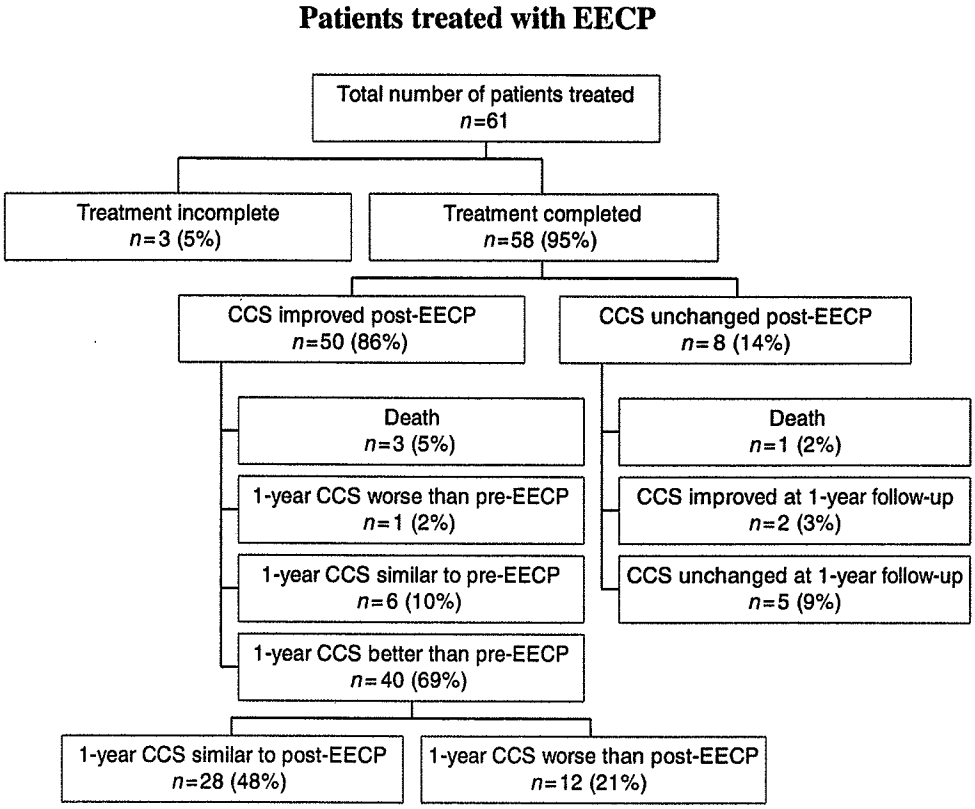

Fig. 1 Immediate and 1-year follow-up angina status assessed by using Canadian Cardiovascular Society (CCS) angina grading.

patients (47%) immediately post-EECP and 26 patients (49%) at 1-year follow-up ($P < 0.0001$). Immediately post-EECP, 47 patients (81%) reported a reduction in the amount of their weekly on-demand GTN use. Overall, the median weekly GTN use was reduced from 7 (2–16) to 0 (0–2) times per week ($P < 0.0001$). At 1-year follow-up, the median weekly GTN use was 1 (0–11) times per week ($P < 0.0005$; Table 2 and Fig. 2c). Thirty-eight patients (70%) required less on-demand GTN at 1-year follow-up than they did prior to EECP. A similar pattern was observed in the 42 patients who did not suffer any cardiac event at 1-year follow-up.

Exercise treadmill testing

Only data from 48 (81%) patients were available. Data from 10 patients were excluded as they had not been exercised consistently using the same protocol. Within 2 weeks after EECP, the mean exercise time had improved from 300 (128) to 384 s (151) ($P < 0.0001$). Thirty-five patients had a repeat exercise treadmill test 3–6 months after EECP. The improvement in exercise tolerance was sustained with a paired mean increase in exercise time of 92 s (79) (30%) at 2 weeks and 105 s (87) (34%) at 3–6 months. However, the mean rate-pressure products at peak exercise were not significantly different with 16 878 (3433) at baseline, 17 677 (3895) at 2 weeks and 17 949 (3911) at 3–6 months.

Medications

Most patients were taking a beta-blocker (75%), lipid-lowering agent (84%), long-acting nitrate (80%), calcium channel blocker (66%) and nicorandil (56%). About 33% were taking an angiotensin-converting enzyme inhibitor. Changes in regular oral medication were deliberately avoided during the course of EECP to avoid confounding the observation and therefore no significant change in the post-EECP

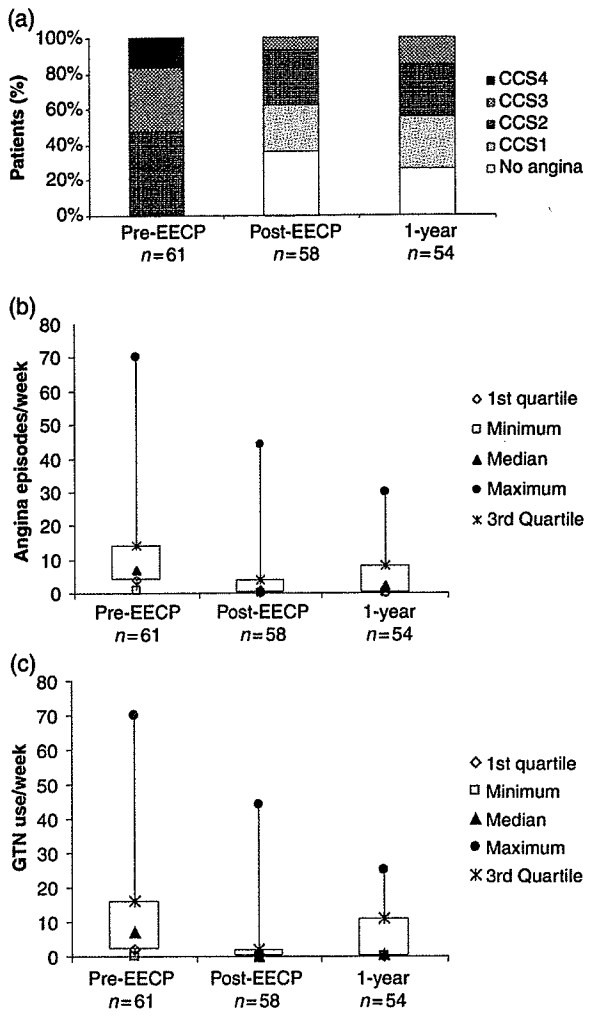

Fig. 2 Overall (a) Canadian Cardiovascular Society (CCS) angina class, (b) weekly angina frequencies and (c) weekly on-demand GTN requirement at baseline, within 2 weeks post-enhanced external counterpulsation (EECP) and at 1-year follow-up.

medications. However at 1-year follow-up, fewer patients were taking calcium channel blocker (66% vs. 52%, $P < 0.05$) and long-acting nitrate (80% vs. 65%, $P < 0.05$) (Table 2).

Adverse events

During treatment, one patient suffered from an MI and two patients' pacemakers interfered with the triggering mechanism of the EECP treatment device. Their treatment course was terminated prematurely. One other patient was found to have paroxysmal atrial fibrillation, which did not interfere with his treatment course. However, 13 patients (21%) reported minor adverse events including leg discomfort in three (5%), skin bruises and blistering in seven (11%), and intermittent ankle oedema in three (5%). One patient reported an increase in her abdominal incisional hernia.

During the follow-up period, 16 patients (28%) had 21 cardiovascular events and 13 cardiac hospitalizations. The mean time to the first cardiovascular event was 200 days (77) after completion of EECP treatment. Four patients (7%) had died and of them two (3%) had MI, one had refractory ventricular tachycardia and one died of worsening heart failure following development of diverticular abscess of sigmoid colon. One patient requested a course of repeat treatment for worsening angina 9 months after completion of the first course. The cumulative 1-year event rates for unstable angina, MI, PCI, CABG, major adverse cardiovascular event (death/MI/CABG/PCI), exacerbation of heart failure and new dysrhythmias were 12%, 3%, 5%, 7%, 19%, 3% and 3% respectively. The event-free survival rate was 72%.

Factors predicting favourable response at 1-year follow-up

A favourable response was defined as being in CCS 2 or less, at least 1 CCS class better than pre-EECP and free of any cardiovascular event at 1-year follow-up. As three of 10 patients who were still candidates for further revascularization received EECP treatment whilst considering CABG, the logistic regression modelling was adjusted for these patients. Using univariate analysis, an immediate improvement of CCS by at least two classes predicted a favourable response (OR 3.90; 95% CI 1.20–12.70, $P < 0.05$), whilst the presence of history of heart failure and hypertension predict a less favourable outcome (OR 0.20; 95% CI 0.06–1.0, $P < 0.05$ and OR 0.20; 95% CI 0.05–0.60, $P < 0.05$ respectively). A similar pattern was observed in multivariate analysis (OR 4.0; 95% CI 0.03–0.60, $P < 0.05$, OR 0.20; 95% CI 0.06–1.0, $P < 0.05$ and OR 0.1; 95% CI 0.03–0.60, $P < 0.05$ respectively). Others baseline factors such as age >65 years, sex, LVEF <35%, diabetes mellitus, hypercholesterolaemia, current or previous smoking history, prior MI, prior PCI and/or CABG, CCS angina grade and medications did not affect the outcome at 1 year.

Discussion

Our study shows that most patients with angina refractory to conventional therapy report symptomatic relief and increase their exercise capacity both in the short- and long term that lead to a reduction in the need for pharmacological therapy. These observations are consistent with data from a randomized controlled trial and observational data from the US [6, 7, 9–12]. The International EECP Patient Registry (IEPR) suggests a sustained improvement in angina and quality of life in the majority of patients over 2 years [13] and an observational study has reported that the benefits may be sustained for 5 years [14].

Although our trial was not a randomized controlled trial, it should be viewed in the context of the nature of the patients recruited. These patients had failed to respond to, tolerate or be accepted for conventional treatment for their angina. Accordingly, a major and sustained placebo-response appears unlikely. There is a paucity of randomized controlled trials showing that alternative, more expensive or invasive, treatments including high-risk repeat revascularization, spinal cord stimulation, left stellate ganglion blockade, thoracic sympathecotomy, and myocardial laser revascularization that might be considered for these patients are effective.

Despite improvements in exercise tolerance, the mean peak heart rate and blood pressure product did not increase as observed in previous studies. This suggests that EECP improves exercise tolerance without an increase in myocardial oxygen consumption [12, 15], which may reflect improved peripheral vascular function, an effect similar to that of exercise training. Other observational studies have noted increases in the time to exercise-induced ST-segment depression, a reduction in dobutamine stress echocardiograhic assessment of wall motion abnormalities and improved myocardial perfusion on both positron emission tomography and radionuclide imaging during exercise after completion of a course of EECP [6, 12, 16–18]. These data suggest that EECP not only improves the symptom of angina but also reduces myocardial ischaemia during stress. These effects may be mediated by improvements in endothelial function [19, 20], neuro-endocrine activation [17, 18, 21, 22], neo-angiogenesis [23] and myocardial oxygen metabolism in ischaemic myocardium [24] leading to improved peripheral and coronary vascular function and an improvement in the coronary collateral circulation. An important placebo effect associated with device therapy may also contribute to patients' improvement, as might occur with any other therapy for patients with intractable angina.

As might be anticipated, patients with medically refractory angina had a relatively high rate of events over a 1-year follow-up and it is not clear that EECP alters these rates [11]. Randomized controlled trials, if patients are willing to forgo the symptom benefit of EECP, would be required to demonstrate whether this rate of events differ from that which occurs in the natural history of the condition. There are few data on the prognosis of patients suffering from chronic refractory angina. Studies investigating other modes of treatment for refractory angina have reported annual mortality of 5–17%, similar to that observed in our study (7.8%). A prospective multi-centre, randomized, controlled trial had reported that EECP combined with drug therapy reduced the risk of cardiac events at 1 year compared with drug therapy alone in patients with ischaemic heart disease [25]. A report comparing PCI candidates treated with EECP in the IEPR to patients who received elective PCI in The National Heart, Lung, and Blood Institute Dynamic Registry of Coronary Interventions has shown similar morbidity and mortality rates over 1 year [26].

The absence of a prior history of heart failure and hypertension and an immediate improvement of angina by at least two CCS grades predict a favourable long-term outcome in our patients. This is consistent with a recent report from the IEPR [27]. That patients with heart failure generally have a worse outcome is not surprising. A recent randomized controlled trial has suggested that EECP may improve symptoms and exercise capacity in patients with heart failure [28]. Although, hypertensive patients gain similar degree of angina reduction when compared with nonhypetensive patients, they have higher 6-month cardiovascular event or repeat EECP rates [29]. Patients with left main coronary disease who did not have a CABG had higher mortality rate than those who had a CABG or those who did not have left main coronary disease 6 months after EECP treatment [30].

Our study is not large. However, it had satisfactory power to detect any clinically significant change in the frequencies of weekly angina and GTN use. Although our study is an observational single centre study, but the effect on symptoms is consistent with the observations of others and with randomized controlled trials [6, 7, 9, 10]. However, there is a paucity of data on medium- or long-term objective benefits such as sustained improvement in exercise tolerance shown in our study. To date, there are only two other observational studies reporting medium-term (6-month follow-up, $n = 175$) [12] and long-term (3-year follow-up, $n = 18$) [31] effect of EECP on objective markers of myocardial ischaemia. Further, most published data are limited to patients from the USA. Patients, healthcare systems and patient expectations may be different in Europe [32, 33]. To our knowledge, this is the largest long-term outcome report by a single European centre. The nature of EECP treatment administration makes a true placebo-controlled study difficult. Therefore the extent of placebo effect could not be adequately assessed. However, the associated sustained improvement in exercise tolerance and reduction in the use of long-acting nitrate and calcium channel blockers in our study are suggestive of treatment effect. Moreover, from a patient perspective, the treatment worked whilst others had failed. Meeting the otherwise unmet needs of patients has considerable merit as an outcome even if the mechanism of benefit is in dispute. Some useful adjunctive investigations such as radionuclide perfusion scans, positron emission tomography and wall motion assessment would further support the treatment effect of EECP. Though these were not performed in our study, consistent positive treatment effect has been shown in other studies [16, 17, 31].

Conclusion

Our study shows that most patients with angina refractory to conventional therapy report symptomatic relief and increase their exercise capacity both in the short- and long term that lead to a reduction in the need for pharmacological therapy. EECP is non-invasive and acceptable to the majority of patients. Further randomized controlled trials and comparative studies against other available treatment modalities would be desirable.

Conflict of interest statement

J.G.F.C. received research funding from Vasomedical Inc., Westbury, NY, USA. No conflict of interest to report for the other authors.

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Correspondence: Dr Poay Huan Loh, Academic Cardiology Department, University of Hull, Hull Royal Infirmary, Hull HU3 2JZ, UK. (fax: +44 1482 675922; e-mail: huan.loh@hey.nhs.uk).