The Benefits and Safety of External Counterpulsation in Symptomatic Heart Failure

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Abstract

Background: External counterpulsation is a safe and effective method of alleviating angina pectoris, but the mechanism of benefit is not understood.

Objectives: To evaluate the safety and efficacy of external counterpulsation therapy in heart failure patients.

Methods: Fifteen symptomatic heart failure patients (subsequent to optimal medical and device therapy) underwent 35 hourly sessions of ECPT over a 7 week period. Before and after each ECPT session we performed pro-B-type natriuretic peptide and brachial artery function studies, administered a quality of life questionnaire, and assessed exercise tolerance and functional class.

Results: Baseline left ventricular ejection fraction was 28.1 ± 5.8%. ECPT was safe and well tolerated and resulted in a reduction in pro-BNP levels (from 2245 ± 2149 pcg/ml to 1558 ± 1206 pcg/ml, $P = 0.022$). Exercise duration (Naughton protocol) improved (from 720 ± 389 to 893 ± 436 seconds, $P = 0.0001$), along with functional class (2.63 ± 0.6 vs. 1.93 ± 0.7, $P = 0.023$) and quality of life scores (54 ± 22 vs. 67 ± 23, $P = 0.001$). Nitroglycerine-mediated brachial vasodilatation increased (11.5 ± 7.3% vs. 15.6 ± 5.2%, $P = 0.049$), as did brachial flow-mediated dilation (8.35 ± 6.0% vs. 11.37 ± 4.9%, $P = 0.09$).

Conclusions: ECPT is safe for symptomatic heart failure patients and is associated with functional and neurohormonal improvement. Larger long-term randomized studies with a control arm are needed to confirm these initial encouraging observations.

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External counterpulsation is an approved therapeutic modality for angina pectoris [1] that is refractory to anti-anginal medications and not amenable to conventional revascularization. Although ECPT has been consistently safe and effective in alleviating angina pectoris, the mechanisms of benefit remain obscure [2]. ECPT is beneficial in terms of exercise time [3], time to ST-depression, and improved stress nuclear studies, parallel with the patient's subjective improvement of functional class and quality of life [4]. The benefits (as assessed by radionuclide stress testing and quality of life measures) may be sustained for up to 5 years [5].

ECPT = external counterpulsation therapy
BNP = B-type natriuretic peptide
HF = heart failure
LVEF = left ventricular ejection fraction

Less is known about the benefits of ECPT in acute and chronic heart failure. In patients with ischemic cardiomyopathy, improved myocardial perfusion may result in both angina and HF relief. Since ECPT can increase nitric oxide levels and reduce endothelin-1, it may favorably affect patients with HF by means of an independent (non-anti-ischemic) mechanism. Strobek et al. [6] confirmed the safety and efficacy of ECPT for angina relief in 466 patients with left ventricular ejection fraction < 35%, who enrolled in the International Enhanced Counterpulsation Registry. Angina relief was unrelated to the extent of left ventricular dysfunction. These benefits were sustained for 2 years post-ECPT [7]. Lawson and colleagues [8] obtained 6 month follow-up data on 1957 patients listed in the international EECP registry (International Enhanced Counterpulsation registry) from 102 participating centers. The 548 patients who had a history of HF were more likely to experience worsening HF (5.5% versus 0.2%, $P < 0.001$) and more inclined not to complete the full ECPT course (22.1% vs.13.8%, $P < 0.001$). During the 7 week course of ECPT therapy, HF patients experienced a similar incidence of major adverse cardiac events: i.e., death, myocardial infarction, revascularization (2.4% versus 1.7%, P = NS). Angina class improved in 68% of the HF patients (compared to 75.1% of non-HF patients, $P < 0.01$). Most (82%) event-free HF patients maintained their angina class at 6 months follow-up.

The aim of the present study was to assess the effects of ECPT on symptomatic heart failure patients with severe left ventricular systolic dysfunction who were optimally treated and revascularized. Besides the subjective improvement reported by the patients (by patient-reported quality of life questionnaire and functional class), we were seeking objective evidence of improvement (as expressed by exercise tolerance, and pro-B-type natriuretic peptide levels, and endothelial function as assessed by brachial flow studies).

Patients and Methods

Patients

Patients with symptomatic heart failure were referred to this study from the hospital heart failure clinic. Included were patients with New York Heart Association class 2–4, and LVEF ≤ 35% documented by echocardiography. Patients who were candidates

for coronary revascularization, electrical or mechanical HF interventions, or experienced HF exacerbation < 30 days prior to enrollment were excluded. We also excluded patients with severe stenotic-valvular heart disease, significant pulmonary disease, alcohol or drug abuse, and severe systemic or terminal illness. Patients unsuitable for ECPT (not in sinus rhythm, altered mental status, and other absolute contraindications for ECPT) were not enrolled.

Study protocol

Subsequent to Institutional Review Board approval, enrollment began in January 2003. Based on inclusion criteria, patients were referred to the study by the heart failure clinic. Medical history, physical examination and informed consent were obtained prior to enrollment; along with baseline electrocardiography, echocardiography and Doppler study of the heart, chest X-ray, complete blood count and chemistry. Patients participated in a run-in period of optimal medical and device therapy (duration 37 ± 17 days) in which medical therapy and electrical device settings were optimized; however, no new devices (pacemakers, cardioverters, defibrillators) were implanted. Medications and device settings were maintained > 2 weeks (mean duration 22 ± 5 days) prior to study initiation, and for the entire study period. Baseline (pre-ECPT) pro-BNP, quality of life (SF-36), NYHA class (by patients and physician), exercise duration (by Naughton protocol), brachial artery flow studies (flow-mediated dilatation and response to nitroglycerine) were obtained. Subsequently, patients underwent 35 ECPT sessions of 1 hour (5 sessions per week) given over 7 weeks using the CardiAssistTM ECPT device (Cardiomedics, Irvine, CA, USA), aiming at maximal diastolic augmentation pressures, gated to ECG and adjusted according to pulse-oxymetry curve. At the conclusion of the 35 ECPT sessions, pro-BNP, NYHA class, quality of life, exercise tolerance and brachial flow studies were performed again employing the same protocols.

NYHA class

Patient's NYHA class was determined by a questionnaire, while physician's NYHA class was determined by an average score of two physicians managing the patients.

Pro-BNP

A 10 ml fasting early-morning sample was obtained in a reagent free tube and spun in a centrifuge (Labofuge 400R, Haraeus, Hanover, Germany) at 3000 rpm for 10 minutes. The serum was removed and shipped to an external core laboratory that stored the sample at a temperature of -23°C. The pro-BNP samples were analyzed by Elecsys 2010 System (Roche Diagnostic, Basel, Switzerland).

Brachial artery function protocol

This was executed by an independent core lab (Sheba Medical Center, Tel Hashomer, Israel) blinded to patients' data using a 15-6 MHz linear array (15-6L HP) ultrasound (HP SONOS 5500 cv-system, Agilent Technologies, Inc., Andover, MA, USA). The protocol consisted of the following:

- E*ndothelium-dependent flow-mediated dilatation*. Vessel diameter measured before and after 1 minute after deflation of a forearm pneumatic tourniquet (which was inflated 5 minutes at pressure > 50 mmHg above systolic blood pressure)
- N*itroglycerin-induced* (*non-endothelium-dependent*) *vasodilatation*. Vessel diameter at baseline and 5 minutes following the administration of a sublingual nitroglycerin tablet (Nitrostat, 0.4 mg, Park-Davis).

Quality of life questionnaire (SF-36)

This short-form questionnaire comprised 36 multiple-choice questions that reflect patients' well-being, functional capacity, limitations, disability, suffering, mood attitude and feelings. The minimal and maximal attainable scores were 36 and 153 respectively.

Statistics

SPSS software (Chicago, IL) was used to perform *t*-test pairs of pre- and post-ECPT parameters. Data are presented as mean measurements with standard deviation. Paired samples correlations, mean difference, and 95% confidence intervals were also obtained. *P* value < 0.05 was defined as statistically significant.

Results

Patients

Baseline patients' characteristics, medical therapy and baseline laboratory studies are presented in Table 1. The mean age was 61 (range 44–72), and all were males with ischemic cardiomyopathy; 7 (46.6%) reported ongoing anginal symptoms. Echocardiographic data show that this cohort suffered from severe LV dilation and systolic dysfunction, and that most had at least moderate mitral regurgitation and pulmonary hypertension at rest.

Safety and tolerance of therapy

Of the 18 patients screened and scheduled for ECPT only 15 concluded the full therapeutic course. One patient asked to stop the therapy after one session due to discomfort during the treatment. Two patients did not initiate therapy for other unrelated medical (orthopedic) problems prior to the first ECPT session. We did not exclude patients receiving anticoagulation therapy or patients with symptomatic peripheral arterial occlusive disease or mild-to-moderate pedal edema. All participants tolerated the treatment well and no adverse events were recorded.

Objective assessment of the effect of therapy [Table 2]

Pro-BNP dropped from 2245 ± 2149 to 1558 ± 1206 ($P = 0.022$, correlation 0.606, mean difference between the paired measurements was 591 ± 1973 pcg/dl, 95% confidence interval of the difference was -444.1 to 1626.8).

Exercise duration by Naughton protocol increased from 720

NYHA = New York Heart Association

LV = left ventricular

Table 1. Demographic, clinical, and laboratory characteristics

Demograhic and clinical characteristics	Value
Age* (yrs)	61 ± 9
Males (%)	100
Angina pectoris (%)	46.6
History of myocardial infarction (%)	100
Intermittent claudication (%)	13.3
Diabetes mellitus (%)	40
Hypertension (%)	33.3
Hypercholesterolemia (%)	66.6
Post-coronary artery bypass surgery/percutaneous coronary intervention (%)	40/46.6
History of smoking (%)	33
Permanent pacing (%)	20
Medications	
Aspirin (%)	93.3
Clopidogrel (%)	40
Coumadin (%)	13.3
Beta blocker (%)	93.3
Nitrates (%)	13.3
Calcium channel blocker	0
Amiodarone (%)	26.6
Angiotensin-converting enzyme inhibitor (%)	66.6
Angiotensin receptor blocker (%)	46.6
Digoxin (%)	6.6
Aldosterone blocker (%)	53.3
Statin (%)	100
Loop diuretic (%)	100
Laboratory values*	
LVEF (echo) (%)	28.1 ± 5.8
LV end-diastolic diameter (mm)	63 ± 8
LV end-systolic diameter (mm)	49 ± 11
Left atrial size by planimetry (cm^2)	28.5 ± 6.6
Severity of mitral regurgitation (grade 1–4)	2.6 ± 1.1
Systolic pulmonary artery pressure (mmHg)	37.9 ± 14.7
Heart rate (beats/min)	72.5 ± 13.6
PR interval per ECG (msec)	170 ± 21
QRS axis (degrees)	1.3 ± 63
QRS duration (msec)	120 ± 40
Hemoglobin (g/dl)	13.7 ± 1.6
Serum potassium (mmol/L)	4.7 ± 0.4
Serum sodium (mmol/L)	138.1 ± 3.2
Serum creatinine (mg/dl)	1.4 ± 0.4
Serum glucose (mg/dl)	142 ± 68.4
Serum urea (mg/dl)	54.2 ± 26.6
White blood cells (1000/µl)	7.9 ± 1.28

* Mean ± standard deviation

± 389 seconds to 893 ± 436 seconds (P = 0.0001, correlation 0.831, mean difference 103.8 ± 146.4 seconds, 95% CI 22.2– 184.9 seconds).

CI = confidence interval

Table 2. The effects of ECPT on heart failure

	Pre-ECPT	Post-ECPT	*P*
Pro-BNP (pcg/dl)	2149 ± 2245	1206± 1558	0.022
Exercise duration (sec)	720 ± 389	893 ± 436	0.0001
Quality of life	54 ± 22	67 ± 23	0.001
Brachial flow-mediated dilatation (%)	8.35 ± 6.0	11.37 ± 4.9	0.09
Brachial nitroglycerine dilatation (%)	11.5 ± 7.3	15.6 ± 5.2	0.049
NYHA class (patient)	2.63 ± 0.6	1.93 ± 0.7	0.023
NYHA class (physician)	2.50 ± 0.7	1.68 ± 0.5	0.021

Values are mean ± SD.

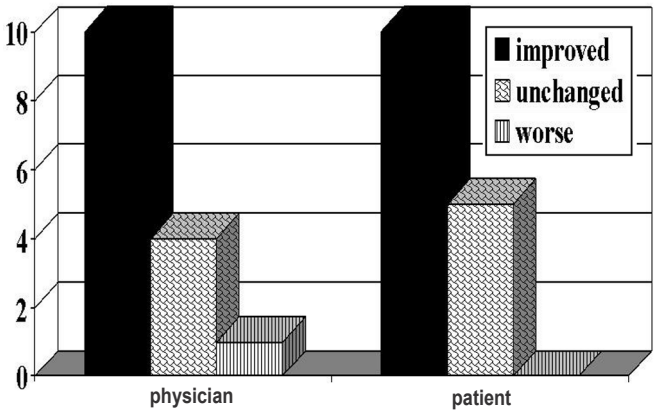

Figure 1. NYHA class change according to physician and patient

Effects of ECPT on brachial artery function

Brachial artery responsiveness to NTG increased from 11.5 ± 7.3% to 15.6 ± 5.2% (P = 0.049, mean difference 4.0 ± 6.48%, 95% CI 0.43–7.61%). Flow mediation dilatation increased non-significantly from 8.35 ± 6% to 11.37 ± 4.9% (mean difference 3.0 ± 5.77%, P = 0.09 95% CI -0.18–6.2%).

Patient's subjective feeling

NYHA class as determined by patients improved from 2.63 ± 0.6 to 1.93 ± 0.7 (P = 0.023, mean favorable class change 0.7 ± 0.59, 95% CI 0.37–1.028). Figure 1 depicts the individual response of patients during therapy (significant change was defined as ≥ 1 NYHA class). Quality of life scores increased numerically from 54 ± 22 to 67 ± 23 (P = 0.001, mean score change 12.6 ± 14.8, 95% CI 4.4–20.8).

Physicians' impression

Physicians also reported a modest non-significant improvement of patients' functional status from 2.50 ± 0.7 to 1.68 ± 0.5 (P = 0.021, mean favorable class change 0.821 ± 0.639, 95% CI .45–1.19).

Discussion

Previous studies suggested that external counterpulsation is safe and effective for alleviating angina in heart failure patients or in

patients with severe LV dysfunction who are suffering predominantly from anginal syndromes [6-8]. However, the benefits of ECPT for the treatment of patients with symptomatic HF due to ischemic cardiomyopathy are not well established.

The safety of ECPT in HF patients was further established in the previously reported PEECH multicenter trial (Presented by Arthur Feldman et al. at the American College of Cardiology meeting, 2005, late-breaking trials, available on the Internet). In PEECH (Prospective Evaluation of EECP in Congestive Heart Failure) the 93 patients who underwent ECPT did not experience more adverse events when compared to the control arm (n=94).

The present study endorses the safety of ECPT in HF patients. From an efficacy standpoint this study shows some encouraging results: patients' exercise tolerance increased and functional capacity along with quality of life improved significantly. Similar improvement in exercise tolerance was reported in PEECH: a 60 second increment in exercise tolerance at 6 months was observed in 35.4% of the ECPT arm and 25.3% of the control group (P = 0.016), while the change in exercise duration at 6 months was 24.7% versus -9.9% (P = 0.01).

Pro-BNP may indicate amelioration of heart failure, ischemia, or both. This clinically significant improvement in pro-BNP levels is consistent with the work of Masuda et al. [9] and Urano et al. [1] who reported that BNP or ANP drops with ECPT.

Both patient-reported functional class and quality of life were improved in our study. A similar effect on quality of life was reported by the PEECH investigators at 3 months, but the benefits were not sustained at 6 months; however, improvement in functional class was sustained at 6 months (31.3 vs. 14.3, P < 0.001).

The brachial flow studies show a trend towards improvement of both endothelial dependent (flow-mediated dilatation) and endothelial independent (nitroglycerine-induced) dilatation. However, in contrast to the study by Shechter and co-authors [11], this report shows enhanced post-ECPT response to nitroglycerine (and to a lesser extent improvement in endothelial dependent flow-mediated dilatation). Bonneti and team [12] showed that ECPT improves endothelial function, as assessed by reactive hyperemia-peripheral arterial tonometry. Other studies showed increased nitric oxide production and reduced endothelin 1 levels with ECPT [13]. Whether any of these measurements is clinically meaningful and bears a long-term effect on the well-being and prognosis of HF patients is not clear at this time.

These encouraging data should be interpreted with caution due to the obvious limitations of our study. Firstly, the study was not randomized and does not have a control (placebo) arm, therefore a placebo effect cannot be excluded as the driving mechanism of improvement. Second, in all parameters of heart failure that were evaluated, the improvement was not uniform; while certain patients exhibited a dramatic improvement with therapy, others did not improve and occasionally even deteriorated. Third, it is not clear whether the beneficial effects obtained by ECPT in HF patients are sustained after discontinuation of therapy, and for how long. Fourth, the study enrolled only men with ischemic cardiomyopathy.

Clearly, a randomized controlled study to assess the long-term safety and efficacy of ECPT in ischemic and non-ischemic cardiomyopathy, with adequate female enrollment, is required.

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