External Counterpulsation Therapy: A Review

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Key Findings

- Success in various medical populations – ECP has been used as health treatment in patients suffering from angina, heart failure, stroke, coronary artery disease and diabetes. It can improve recovery and enhance performance for specific populations, for example in elite athletes.
- Associated risks – As with all treatment methods there are associated risks, side effects and limitations of use. Reported side effects are varied, and the use of ECP is limited for certain populations. This highlights the importance of regulation and guidelines for use.
- Duration and intensity are essential elements – The effectiveness of ECP as a treatment is influenced by both the intensity of the pressure and the duration of the session. Optimally full pressure ECP of 200-300 mmHg is more beneficial than sham (50-75 mmHg). Those who completed the full 30-35 hours of ECP see greater benefits than those who received shorter sessions or did not complete the course.
- External counterpulsation as cost-effective treatment – As a growing area of evidence, ECP may be considered over time as a cost-effective procedure.

Introduction

Enhanced external counterpulsation therapy (ECP) is considered a non-invasive, alternative outpatient treatment for individuals who are not candidates for invasive procedures like surgery[1]. The concept of ECP as a potential medical treatment dates back to the early 1960s[2], yet its study did not gain in popularity until the early 2000s[3]. Of the reviewed literature over 60% of the studies were conducted in the last 10 years, indicating the relatively new acceptance of ECP, and thus an ongoing and growing body of evidence towards it.

ECP is a device consisting of three paired pneumatic cuffs that are applied to the lower limbs. These cuffs sequentially inflate, with applied external pressure of 250-300 mmHg during diastole.[3] The purpose of this is to enhance coronary blood flow in diastole and facilitate left ventricular flow in systole[3], as compressing the vessels of the lower extremities increases venous return[1]. Thus, ECP is believed to develop and recruit small branches of blood vessels, called collateral circulation, around narrowed or blocked arteries. This creation of new collateral flow can increase the blood supply to the myocardium[1], restoring the balance of oxygen supply and demand[4].

As such ECP has been studied as a medical treatment for a variety of health problems associated to the heart and circulatory system, including angina pectoris, chronic heart failure

(CHF), coronary artery disease (CAD) and diabetes type II.

Guidelines for ECP Treatment

The 1999 publication of the Multicenter Study (MUST)-ECP trial which truly introduced the concept of ECP popularly as a performance and health therapy, was the first to set out parameters for the duration and intensity of an ECP trial[2]. Here patients were given 35 hours of either active or inactive counterpulsation, over a 4- to 7-week period.

Intensity remains key to the positive effects of ECP. In more recent literature, these groupings are more commonly referred to as full pressure (active) or sham (inactive) pressure. Full pressure starts at 200 mmHg and increases up to 300mmHg; this maximum pressure is considered to produce the optimal hemodynamic effects[4]. Sham-pressure on the other hand acts like a placebo, with pressure no more than 50-75mmHg, which gives the sensation of treatment without altering arterial hemodynamics[5]. Full pressure/active ECP has been found to result in greater health benefits than sham/inactive ECP, increasing to a greater extent VO2 max[6], forearm and calf blow flow[7], HRQoL[8], and improvements in conditional NIH Stroke Scale[9], as well as reductions in angina symptoms[10].

Duration is equally as important. A fully completed course of ECP treatment that involves 35 1-hour sessions, 5 days a week, over 7 weeks is found to have the most augmented health effects in comparison to those who have received shorter courses[11] or did not complete their treatment[12]. Lin and colleagues (2013) found ECP duration ($p=0.008$) an independent predictor of a favourable functional outcome after ECP treatment, whereby patients who underwent longer treatment duration had better functional outcomes 3 months later. This finding is consistent with studies of patients with angina pectoris where a significantly greater percentage of those who completed one or more sessions saw at least one Canadian Cardiovascular Society (CCS) class reduction compared to those who did not (83.4% vs 21.7% respectively, $p < 0.001$)[12].

Likewise, a study of CAD patients who underwent either 20 sessions of ECP or cardiac rehabilitation (CR) showed no significant changes in measures of HQoL, Plasma Nitric Oxide, Endothelin 1 and High Sensitive CRP after ECP in comparison to CR[13]. This suggests that ECP is not effective at this duration, but potentially could be with more sessions as positive effects were still found[13]. Significant effects have been also found in other studies on CAD patients who attended 30+ sessions[14,6]. Collectively, the literature suggests that a longer ECP duration is more effective.

ECP & Health

The majority of the reviewed literature (82%) focused on the health-related benefits of ECP. It has been studied as a medical treatment in a variety of health problems as explained below.

Angina Pectoris

ECP is most often studied in those with refractory or stable angina pectoris. Angina, chest pain as a result of a lack of oxygenated blood flow to the heart, is thought to benefit from ECP because of its ability to enhance venous return[1]. In particular, ECP can be considered an option for refractory angina, which is not controllable through the use of medication or revascularisations[15].

The standard ECP treatment length of 35 one-hour sessions over a period of 7-8 weeks, has demonstrated positive effects in a variety of different ways for those with both refractory and stable angina. For example, significant effects were seen in CCS class reduction, self-reported pain scores, walking distance, and health-related quality of life (HRQoL) for patients with refractory angina both immediately after ECP and 6 months following[15].

CCS class reduction is often reported as being improved by at least one class post ECP treatment[16,17,18,19,20,21,22]. Several meta-analyses have indicated as such. Zhang and colleagues analysed 1,768 patients with refractory angina and found that angina class improved by at least 1 CCS class in 85% of patients from before to after ECP treatment (95% confidence interval [CI] 0.81–0.88, I2=58.5%, $P<0.001$)[20]. Likewise, Shah and colleagues found in their cohort of 13 studies, of 949 patients, that ECP reduced angina class by at least one CCS score in 86% of the patients (95% confidence interval 82-90%, Q statistic p=0.008][16].

These improvements have been found to be sustained over time. For example, May et al. found that CCS class just after ECP was at least one CCS class lower in 82% of the patients, 3 months after in 79% and 12 months after in 76% (all p=0.0002)[19]. Similar results were found by Wu and colleagues[18] and Lawson et al. [17]. The former found improvement rates in CCS class of 85% immediately after ECP and 66% at 1-year follow-up[18]. The latter saw improvements in 85.1% of patients, whereby 6 months post ECP 19.9% were in the lower classes of CCS III or IV and 26.9% were angina free[17].

For HRQoL, aspects of self-reported improvements in mental health, bodily pain, physical function, role disability due to emotional/physical health, social function and vitality[15] have been shown to improve, and be sustained 3 months post ECP[23]. Improvements in HRQoL have been documented on various occasions whereby ECP treatment groups reported a greater significant improvement than controls 12 months post treatment[22], and with HRQoL being reported as higher in full pressure ECP treatment than sham[8]. This indicates that ECP goes beyond treating physical symptoms, and can benefit psychological symptoms as well.

In fact, the psychological benefits of ECP can be shown in a study of 27 refractory angina patients, where post an ECP course, significant reductions in the General Symptom Index (measuring distress; 0.14+0.03, p=0.001), self-reported depressive symptoms (0.18+0.05, p=0.01), state anxiety (1.95+0.83, p=0.05) and somatisation (0.29+0.09, p=0.01) were seen[24]. This provides evidence supporting the fact that, in the short term, ECP can result in a reduction in subjective assessment of pain, disability and lower levels of reported depression[24]. Further exploration is needed into such effects and their sustainability over the longer term.

> "EECP is a valuable option for patients who were unresponsive to maximal medical management and/or invasive therapy."
>
> *Zhang et al., 2015*

Fewer longer term follow-ups of the effects of ECP exist. However, of those conducted the results are positive. A two year follow up evaluated 1,097 patients from the International ECP Patient Registry. This demonstrated that immediately following ECP, 73% of patients improved by at least one CCS angina class, and those with CCS Class III or IV angina decreased from 86.9% to 26.8%. Improvements of angina symptoms by either one CCS class (74.9%) and decrease in the percentage of those with class III or IV angina (24.1%) was maintained at 2-year follow-up. Additionally improvements in health status (54.5%), quality of life (53.2%), and satisfaction (57.8%) were found and maintained at 2-year follow-up.[25]

Stroke

ECP treatment studied in stroke patients provided an overall positive consensus. A 2008 study[26] found a reduction of 2.1 (95% CI, 1.5 to 2.7) points in the National Institutes of Health Stroke Scale (NIHSS) after a 7-week course of ECP, compared to a lower reduction for no ECP. Similarly, in a more recent randomised control trial (RCT) the effects of ECP on the cerebral blood flow of ischemic stroke patients reported that both sham and full-pressure patients had an improvement in conditional NIHSS of ≥ 2 points within 20 or 50 minutes of ECP initiation (p=0.2138)[9]. However, these significant effects between groups were not sustained at one week and 30 days' post treatment, indicating the need for longer term study in this population.

Longer term effects in stroke patients have been noted up to 3 months post ECP. Lin et al. found a good outcome in 57.5% patients at their 3-month follow-up[11]. While this is initially positive, a single study alone cannot constitute as an evidence body for the longitudinal effect of ECP on stroke patients and more research is required. Interestingly, however, this study also determined that a variety of significant factors influenced this sustained effect, including age (p=0.023; patients in the good outcome group were younger), lower baseline NIHSS scores (p=0.001), and longer duration of ECP (p=0.008). These are found to predict a favourable functional outcome after treatment[11] and may be taken into consideration when studying further.

> "ECP is the only truly non-invasive, atraumatic technique for which clinical anti-ischemic improvements have been shown."
>
> *Braith, Casey & Beck, 2012*

Heart Failure

Initial study in this area indicated that ECP was a promising new therapy for the treatment of heart failure[27]. As individuals on many occasions are not suitable candidates for invasive treatments like angioplasty and grafting, ECP offers a non-invasive alternative[28].

For those with chronic heart failure (CHF), ECP has shown to be beneficial in improving exercise duration, in comparison to a PT control[29]. This was shown to sustain at 6 months, however the mean differences in VO2 max are low (0.30, 95% CI −0.53 to 1.13) suggesting the effect is small. Other studies have also found small non-significant differences[30], indicating this is an area with future potential. More significantly, ECP treatment, compared to a control, results in improvements in memory and cognitive functioning[31], large scale improvements in walking distances[32], and significant improvements in diastolic augmentation for those with CHF[33]. In particular, ECP improved coronary perfusion through significant diastolic augmentation and systolic unloading[22,33].

Coronary Artery Disease/ Ischemic Heart Disease & Blood Flow

In many cases coronary artery disease (CAD) is present in those who have angina, and thus the effects of ECP on reducing angina symptoms have a resulting positive effect on CAD outcomes[28].

Yet a variety of evidence exists for the use of ECP specifically on patients with CAD. In their review, Braith, Casey & Beck[28] found that between full pressure and sham ECP groups, ECP treatment improved flow mediated dilation (FMD) for the brachial and femoral arteries (51%; 39%)[28], which can be supported by further study showing ECP to acutely improve FMD to a greater extent (51%; 68% respectively)[5]. Braith et al. also found ECP to decrease both peripheral and central arterial stiffness in comparison to the sham group[28]. Such improvements in stiffness in the arms and legs, in addition to the vascular region, indicates that ECP can have a whole body effect. This is buttressed by the fact that ECP helped induce anti-inflammatory effects, by reducing proinflammatory cytokines and adhesion molecules, and potentially reducing the risk for future cardiovascular events of those with CAD[28]. Other studies have found similar results whereby ECP has reduced proinflammatory cytokines (TNF-ɑ) in those with angiographic CAD, leading to a reduction in symptoms and the conclusion that ECP provides anti-inflammatory effects[10].

It appears that the intensity (pressure) of ECP is a reoccurring mitigating factor in the success of the treatment for those with CAD, particularly regarding blood flow. For example, ECP at full pressure has successfully shown improvements in forearm (+18%) and calf (+15%) blood flow after 7 weeks of ECP, but not in sham[7]. The same was found in a study investigating the effect of ECP on coronary collateral function, whereby collateral flow index increased significantly (p=0.05) from 0.141±0.060 to 0.201±0.067 after high pressure ECP, but not in low pressure[34]. Although these studies had relatively small sample sizes, the effects are nevertheless supported by the aforementioned improvements in flow mediated dilation, indicating that for CAD patients ECP appears to be a very promising treatment option for enhancing blood circulation.

Diabetes

A few studies have begun to focus on the impact ECP can have on diabetes type II. ECP treatment has been found to help reduce advanced glycation end products (AGEs)[35] and other glycaemic parameters, including fasting plasma glucose, which was sustained for 2 weeks post treatment[36]. ECP has also been found to significantly improve whole-body composite insulin sensitivity index (+54.2 %), and nitrite/nitrate (NOx; +48.4%) 48 hours post treatment[36].

Similarly, a study examined the effects of ECP on individuals with abnormal glucose tolerance, and reported decreases in fasting plasma glucose and the homeostasis model assessment of insulin resistance (HOMA-IR) (31%), alongside an increase in the whole body composite insulin sensitivity index (21%)[37]. These results indicate that ECP had a beneficial effect on management of blood sugar levels, in a similar way to diabetes type II.

Research into the management of diabetes type II is ongoing. Renew therapy and the University of Queensland recently investigated the effect that a 7 week course of 30-40 minutes of ECP can have on diabetes management. This study focused on using ECP to stimulate the effects that physical activity has in regulating blood sugar levels, and looked to measure this through vascular and other health functions[38]. It is believed that like exercise training, ECP will improve circulation by putting peripheral veins and arteries under reduced stress.

Recovery

> "Whilst having this compression between heartbeats it actually promotes the return of blood to the heart which eases the amount of work the heart has to do"
>
> *University of Queensland researcher Llion Roberts*

ECP has also been studied as method for enhancing sport recovery. The Renew Group and the University of Queensland collaborated to investigate this impact specifically in elite male rugby players.

Several 30 minute ECP sessions were found to influence the recovery and stress symptoms of elite male rugby players following a competitive rugby match[39]. Subjective symptoms of stress (DALDA) were significantly better following ECP, and resulted in lower levels of cortisol and higher testosterone: cortisol, reflecting improved recovery and a higher state of anabolism. This hormonal data was supported by improvements in perceived stress symptoms, and overall indicated improved recovery.

In a similar population, Kelly and colleagues[40] examined the longer term effects of ECP on performance improvement alongside cold water immersion (CWI) over a period of 4 weeks. 26 elite rugby players were randomly assigned to either 6 minutes of CWI or 20 minutes of ECP post field training. Subjective perceptions of leg and upper body muscle soreness and well-being were significantly better ($P < 0.05$) following ECP, and over the 4 weeks ($P < 0.01$; 15% and

P < 0.01; 10% respectively) compared to CWI[40]. These results favour the efficacy of regular ECP therapy over CWI on improving measures of recovery in elite athletes.

However, the more specific physiological effects of ECP remained unclear. As a result in 2016, Kelly and colleagues[41] conducted an additional study investigating the influence ECP had on blood pressure, wave forms, and heart rate during either full pressure or sham ECP treatment. Diastolic blood pressure was higher in the ECP condition than the control, both pre-recovery (p=0.007) and post-recovery (p=0.027), and heart rate decreased (p=0.013, 6.7%)[41], suggesting ECP enhanced circulatory performance.

Performance

The least amount of study has been dedicated solely to the influence of ECP on performance.

A single 2013 study investigated the use of ECP as a treatment for attentional and memory capability in patients with chronic heart failure (CHF). Kozdag et al. [31] assigned patients to either a ECP treatment group or a medical control, and found alongside reductions in CCS angina class, those receiving ECP showed a statistically significant improvement in spontaneous naming (p=0.011), forward row score of the attention subset among domains of cognition (p=0.020) and interference time of executive function (p=0.012). Such results suggest that ECP helped improve both short-term memory and cognitive functioning in the short term, over the course of a 7 week treatment course[31].

In regards to physical and exercise performance, ECP treatment has shown to improve functional capacity through improvements in the 6-minute walking test. Most recently Melin et al. demonstrated that maximum walking distance increased by 15%, which is in parity to that achieved after aerobic exercise training in similar patients[32]. This supports previous studies by Wu, Martensson and Broström [15] and Sahlén et al. [42] on angina patients. Both found improvements post ECP treatment with walking distances of +7% and +5% respectively[15,42].

ECP has also shown to improve exercise tolerance after treatments in patients with CAD[43]. Similarly, in patients with refractory angina, significant differences in total exercise time before and after treatment where recorded (p=0.001), a majority of these sustained for 6 months (p=0.010)[44]. This led to the belief that ECP therapy exerts a 'training' effect, decreasing peripheral vascular resistance and the heart rate response to exercise[43].

More recent studies indicate a similar concept. In a 2016 collaborative study between the University of Queensland and Renew Therapy[45], elite rugby players were randomly assigned to 30 minutes of ECP or a placebo, following a 60-minute conditioning training session. Those in the ECP group saw increases in cycling peak power (p=0.028, 11%) and accumulated peak power (p=0.027, 14%) in comparison to the controls. Also found were improved ratios of plasma testosterone: cortisol (p=0.017, 20%) against the control group. This displays a reduction in hormonal indicators of stress associated to exercise, as well as direct improvements on exercise performance[45].

> "Patients report less fatigue while conducting activities of daily living. They also state they are able to carry out leisure activities, such as golf, swimming, and walking with greater enthusiasm, confidence, and stamina."
>
> Brosche et al., 2004

Finally, ECP is associated with myocardial ventricular performance is in those with heart failure[46]. Here the standard 35 hours of ECP treatment demonstrated improvements in left ventricular myocardial performance, left ventricular systolic function and left atrial volume index[46]. This translates to overall improvements in cardiac performance, reducing the chance of adverse clinical events.

Cost-Effectiveness

Recently, in 2015 Lawson and colleagues[17] observed the cost-effectiveness of ECP in reducing hospital costs in the USA, for those with for refractory angina. The improvements in CCS class as a result of ECP 6 months' post treatment was calculated to reduce hospitalisations by 1.22 visits per patient per year. This would result in an annual cost savings per patient of $17,074, translating to a reduction in hospitalisation costs of approximately $512million[17].

Within the UK, according to the National Institute for Clinical Excellence (2004), ECP is cost-effective if health-related QoL (HRQoL) is sustained for more than a year and throughout the patient's life. McKenna et al.[22] calculated the incremental cost-effectiveness ratio (ICER) of ECP as £18,643 per additional quality-adjusted life-year (QALY). This falls below the conventional annual estimated cost of £20,000-30,000 per year[22], which could save up to £11,357 annually. However, due to the low probability of ECP being effective over no treatment (0.44) it is unlikely to be cost-effective unless the HRQoL benefits are sustained throughout one's lifetime. If this is the case, the ICER decreases to only £5,831 per year, with a probability of 96% effectiveness, saving a total of between £14,169-24,169 per year[22]. It appears that cost-effectiveness is highly dependent on the duration of the QoL benefits. At present a small, yet promising, body of evidence existing clarifying the cost-effectiveness of ECP, which requires further, potentially longitudinal, study[47]

Limitations, Risks & Safety

Despite the apparent benefits of using ECP, like all treatments, it is not without its risks and side effects. ECP is appropriate for a specific population of people. This can be, for example, patients with symptomatic CAD or refractory angina, who may respond poorly to medical treatment or are unable to undergo angioplasty or bypass graft surgery[48,15], or interventional or surgical revascularisation[49,15].

Contraindications exist for those with types of valvular heart disease (especially aortic insufficiency), for those with recent cardiac catheterisation, an irregular heart rhythm, significant blockages in the leg arteries, or a history of deep venous thrombosis[49]. Precautions also exist for those with severe hypertension, as the process of raising the diastolic pressure even higher during ECP could cause excessive heart strain[48]. Likewise, ECP was considered dangerous for individuals with LVD and severe peripheral arterial disease, although both these populations have been treated successfully with ECP show casing low morbidity and increased exercise tolerance[4]. It would appear that these populations are where close monitoring is needed to ensure safety, and such monitoring may open up options for further ECP use.

Side effects of full pressure ECP range from mild to severe dependent on the patient population. Mild side effects such as a need to urinate in patients with ischemic stroke have been reported[9], while other studies indicate more severe effects such as back and leg pain and superficial skin lesions in patients with CAD[4], and bruising, pain and swelling in those with angina[30]. It should be noted that the studies reporting severe side effects are over 10 years old, with many more recent studies reporting on the safety of the ECP treatment.

For example, variations in the equipment generated a novel ECP system, Compact CP, which was piloted on those with CHF. Its feature was a double-lumen cuff that aims to reduce the impact of cuff inflation[33]. The pilot was successful in aiding coronary perfusion improvements alongside comfort at low pressure (40 kPa). Although comfort was decreased at high pressure (50–70 kPa), no adverse effects were reported. ECP has since demonstrated to be a safe, non-invasive treatment for patients with stable angina and Aortic Stenosis (AS) [21] and stroke [9], among others

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