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EECP: A non-invasive therapy for refractory angina

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What is enhanced external counter pulsation therapy?

Which patients are suitable for this treatment?

What are the benefits?

REFRACTORY ANGINA IS A CHRONIC AND OFTEN DISABLING CONDITION, WHICH may be demoralising for both patients and their carers.[1] Those affected may have endured complex pharmacological treatment, recurrent hospital admissions, repeated investigations and multiple interventions. Patients with refractory angina have by definition exhausted conventional pharmacological and interventional treatments.

Initial symptom relief in chronic stable angina is often successful, but for a significant minority, symptoms may not be alleviated or will recur in time. Intervention is increasing both in the management of acute coronary syndromes and chronic stable angina and so too is the need for repeated intervention, where the complexity and procedural risk may be increased as well as the psychological and traumatic burden to patients of increasing age and morbidity.

Furthermore multiple coronary stenting may diminish the possibility of surgical intervention by metallising arteries. Increasing longevity and the resulting demographic shift in age and the uncertainty of long-term results of intervention may also exacerbate these problems in the future.

The incidence of refractory angina has been estimated at around 25,000-75,000 new cases per annum in the USA[2] where there are more than two million interventions each year, with a half-life to re-intervention of seven years. These numbers are likely to increase as intervention increases and the survival of vascular patients improves. Many strategies are available, some exemplified by the treatment offered by the National Refractory Angina Centre in »

Liverpool, the only specialist centre in the UK. These include support, education and psychological approaches to diminish the counterproductive effects of fear and anxiety on pain. Analgesia is seldom effective and potent analgesia may be inappropriate except in the small number of patients who may be approaching the end of life.

Alternative means of managing coronary disease, especially for patients who develop angina refractory to conventional treatments, or those who are unable to tolerate or choose not to proceed with such treatments, are urgently needed.

ENHANCED EXTERNAL COUNTER PULSATION

Counter pulsation is a therapy developed from sound physiological principles,[3] widely used in cardiothoracic and interventional centres in the form of intra-aortic balloon pumping (IABP). It has now been developed externally as enhanced external counter pulsation (EECP), see box 1 below.

EECP is a non-invasive, safe and well tolerated therapy, with very few contraindications. It was approved by the FDA in 1995 for the treatment of stable angina, unstable angina, cardiogenic shock and MI and, in 2002, heart failure.[6] The American Heart Association recommends it as a class 11b intervention for treating refractory angina. EECP is also included in the SIGN guidelines on managing refractory angina. Currently, EECP is used predominantly in patients with severe angina, who are at high risk and are not suitable for revascularisation. It provides a therapeutic and supportive approach to managing such patients regardless of age[7] and co-morbidity including those with stable heart failure.[8]

The treatment is most often undertaken in an outpatient setting. In the USA, where currently 20,000 patients are treated annually in around 1,000 centres, it is most commonly directed by cardiac interventionists.

The recommended duration of treatment of 35 hours (one to two hours daily for three to seven weeks) is based on the results of pilot studies indicating increasing symptomatic benefit up to this time and little further benefit beyond. Researchers are currently looking at different 'dosages' of treatment, especially in heart failure, including top up regimens. Optimisation of treatment may depend on the degree of diastolic augmentation achieved.[9]

BENEFITS

EECP is undoubtedly therapeutic, in the sense that myocardial perfusion has been shown to increase both acutely and in the longer term following treatment. This has been demonstrated by radio-nuclear scanning,[10] PET scanning,[11] time to onset of ischaemia on exercise testing,[12] stress echo[13] and most recently by cardiovascular MR.[14]

EECP unlike interventional treatments can be shammed and therefore subjected to randomised controlled trials (RCTs). The first RCT, MUST EECP[12] reported improved symptoms and exercise time to onset of ischaemia and a sub-study reported improved quality of life scores one year after treatment.[15] We have recorded improvements in quality of life at two years and have submitted our findings for publication.

Patients with refractory angina frequently have impaired LV function, both systolic and diastolic, as well as poor physical conditioning through lack of exercise. They may find their breathlessness on exertion and fatigue even more distressing than their angina, especially once the fear of this symptom is overcome. EECP may be effective in improving these symptoms as well as reducing angina. Furthermore, psychosocial benefits e.g. feeling of wellbeing and reduction in depression, are significantly improved in subjects with and without objective measures of improved ischaemia.[16]

Patients with refractory angina often have very advanced ischaemic heart disease and the majority will have significantly impaired LV function.[1] EECP increases venous return but is well tolerated and safe in these patients provided treatment is commenced at high pressure, which provides maximal after-load reduction on cuff deflation, when the vascular beds in the lower limbs are relatively empty.[17]

The international EECP patient registry has published follow-up data at two years[18] and three years,[19] showing sustained symptomatic benefit in the first cohort of 5,056 patients. Immediately following treatment the numbers in Canadian Cardiovascular Society (CCS) class III and IV had declined from 89% to 25%, 78% had improved by at least one CCS class and 38% by two classes, see table 1, below. These benefits were sustained in 74% of patients at three years with 35% of patients reported to be free of angina. Improvement in quality of life scores at one year and exercise tolerance and myocardial perfusion over five years[20] have also been documented.

Favourable long-term outcome defined as sustaining CCS class II or

Box 1

Enhanced external counterpulsation therapy (EECP)

- This therapy provides augmentation of diastolic flow, through sequential inflation and after-load reduction by simultaneous deflation, from a series of three cuffs applied to calves, lower thigh, upper thigh and buttocks.
- The cuffs are inflated to a maximum cuff pressure of 280mmHg, gated to the ECG and the degree of diastolic augmentation monitored plethysmographically.
- This systolic unloading and diastolic augmentation results in an increased pulsatile flow throughout the circulation.
- Coronary blood flow measured by flow wire,[4] increases substantially and diastolic arterial wall shear stress has been shown to increase more than twofold. These effects are greater than those achieved by IABP, [5] and cannot be achieved pharmacologically.

Table 1

Angina: Canadian Cardiovascular Society (CCS) classification system

Class I	No angina with ordinary physical activity such as walking, climbing stairs - angina occurs with strenuous, rapid or prolonged exertion
Class II	Slight limitation of ordinary activity - angina occurs on walking or climbing stairs rapidly, walking uphill, physical activity after meals, or in cold, or in wind
Class III	Marked limitations of ordinary physical activity - angina when walking at a normal pace in normal conditions
Class IV	Inability to carry out any physical activity without discomfort - anginal symptoms may be present at rest

Box 2

Mechanisms of benefit

- Possible mechanisms include improved endothelial function[27,28] promotion and recruitment of collaterals,[17] reduced arterial stiffness,[29] improved systolic and diastolic function,[30] neurohumoral[31] and metabolic effects,[32] peripheral effects of lower body exercise [33] and non-specific effects e.g. psychological and supportive benefit during the course of treatment.
- Growing experimental evidence suggests that EECP may exert its clinical benefits via the effects of shear stress on endothelial function. EECP has been shown indirectly through measures of vascular reactivity to improve endothelial function in patients with angina.[34]
- EECP has also been shown to have anti-inflammatory effects in patients with symptomatic angina significantly decreasing pro-inflammatory biomarkers and a favourable effect on pro-inflammatory cytokine and adhesion molecule expression and signalling.[35]
- Endothelial dysfunction is increasingly recognised as the bridge between vascular risk factors and the atherosclerotic disease process. EECP may provide a means of preventing this pathological progression, especially in those who are unable or unwilling to exercise adequately.

Table 2

Contraindications to EECP

- Haemodynamically significant aortic valve regurgitation
- Abdominal aortic aneurysm requiring intervention
- Recent history of venous thromboembolism
- Severe pulmonary hypertension
- Poorly controlled systolic hypertension
- Major bleeding diathesis
- Pregnancy
- Bilateral amputees (the skin in contact with the cuffs should be intact and healthy)

less and without major adverse cardiac events (MACE) was achieved in 36%. These results are similar to those for PCI documented in the NHBI registry for patients with comparably severe symptoms (CCS III and IV), where the combined endpoint for recurrent angina plus MACE at one year was 47%.[21]

'EECP is a non-invasive, safe and well tolerated therapy, with very few contraindications'

EECP is as effective in women,[22] patients with diabetes,[23] the obese[24] and the elderly (>80 years)[7] and although much of the data originates from the USA encouraging results have recently been published from the UK.[25]

Rehabilitation is likely to be important, especially in reinforcing the benefit of treatments that can improve exercise tolerance, such as EECP, but as yet there are no specific guidelines for rehabilitation in refractory angina.[1]

There are of course palliative treatments which have a role in diminishing pain, e.g. TENS, but others e.g. nerve blocks and spinal cord stimulation, are invasive and perhaps not ideal for patients who have undergone many procedures and being palliative are neither likely to benefit circulatory function directly and diminish the fatigue and dyspnoea which are prominent symptoms in refractory angina, nor to have a vasoprotective effect. Surgical and percutaneous transmyocardial revascularisation are now seldom recommended owing to the operative risks and uncertainty of benefit.

EECP however, provides not only a safe, well tolerated and therapeutic treatment for these patients, but also facilitates a supportive approach through 35 hours of therapy. It improves fitness through passive lower body exercise and often an improvement in wellbeing which may relate to an effect of therapy delivered to the entire circulation. Other benefits include the potential to reduce erectile dysfunction,[26] which is so prevalent and disabling in patients with vascular disease.

The exact mechanism by which EECP exerts its clinical benefits is not fully understood but is likely to be complex and multifactorial, see box 2, above.

PROGNOSIS

Prognostic benefit from EECP has not yet been evaluated in long-term, randomised outcome studies. However, a preliminary report at one year from an RCT of EECP added to optimal medical therapy, has shown reduced mortality and MI rates.[36] A protective effect over five years, has been suggested in a non-randomised consecutive study of EECP compared with standard pharmacological treatment.[37] Data from the IEPR,[18] indicate a three-year mortality rate (15%) comparable to that for high-risk patients with non-prognostic lesions treated by CABG.

Non-responders to EECP are identified as a particularly high-risk group, whereas responders, despite their high-risk profile, appear to have a better than expected prognosis.[38] A comparison of those completing EECP treatment with the 14% failing to complete treatment, but surviving beyond 60 days, has shown a significantly lower mortality and MACE.[39] A comparison of radionuclide responders to EECP versus non-responders, has also shown a significantly lower MACE rate at five years.[20]

Outcome following either EECP (IEPR) or PCI (NHIBI dynamic registry) has been compared using two cohorts of PCI candidates treated for stable angina.[40] Although symptom relief was greater with PCI, one-year survival and re-intervention rates were comparable, despite the EECP group being slightly older and having significantly higher risk with more CCF, diabetes, prior intervention and lower ejection fraction.

These findings indicate that it would be worthwhile undertaking comparative outcome studies in stable angina, either versus intervention or with adjunctive use of EECP. A three-pronged study comparing outcomes of treatment by EECP, medical treatment and PCI in chronic stable angina is planned in China.

LIMITATIONS

EECP is not suitable for every patient although there are few absolute contraindications. See table 2, above.[41] »

key points

SELECTED BY

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Intervention is increasing both in the management of acute coronary syndromes and chronic stable angina and so too is the need for repeated intervention, where the complexity and procedural risk may be increased as well as the psychological and traumatic burden to patients of increasing age and morbidity.

Enhanced external counter pulsation (EECP) is an alternative means of managing coronary disease. This therapy provides augmentation of diastolic flow, through sequential inflation and after-load reduction by simultaneous deflation, from a series of three cuffs applied to calves, lower thigh, upper thigh and buttocks.

Currently, EECP is used predominantly in patients with severe angina, who are at high risk and are not suitable for revascularisation. It provides a therapeutic and supportive approach to managing such patients regardless of age and comorbidity including those with stable heart failure.

Treatment is carried out daily on an outpatient basis for a total of 35 hours over three to seven weeks. RCTs have reported improved symptoms and exercise time to onset of ischaemia. Improved quality of life scores have been reported two years after treatment.

EECP provides not only a safe, well tolerated and therapeutic treatment for these patients, but also facilitates a supportive approach through 35 hours of therapy. It improves fitness through passive lower body exercise and often an improvement in wellbeing which may relate to an effect of therapy delivered to the entire circulation. Other benefits include the potential to reduce erectile dysfunction, which is so prevalent and disabling in patients with vascular disease.

There are relatively few absolute contraindications. These include, haemodynamically significant aortic valve regurgitation, abdominal aortic aneurysm requiring intervention, recent history of venous thromboembolism, severe pulmonary hypertension, poorly controlled systolic hypertension and major bleeding diathesis.

Provision of EECP should be considered as part of a dedicated service for patients with refractory angina. This service should ideally offer a careful diagnostic assessment and a multidisciplinary approach, including psychological support and rehabilitation and in those with a continuing burden of symptoms the freedom to choose between a psychological approach with CBT, a therapeutic approach with EECP and palliative treatments that can be offered by pain specialists.

Growing experimental evidence suggests that EECP may exert its clinical benefits via the effects of shear stress on endothelial function. Combined with optimal medical therapy EECP has been shown to reduce mortality and MI rates and provide a protective effect over five years.



Case history

EECP - a success story

The patient in the picture, with therapist Pat Moore, had refractory angina. His symptoms were so unstable that he was unable to leave hospital. After undergoing treatment with EECP he was soon discharged home where he was able to look after his disabled wife for the next 18 months. She would otherwise have had to have gone into care. At the time of treatment the patient was the oldest person to be treated by the authors in Bradford.

They are planning to develop a refractory angina service in Bradford based around EECP. They have managed around 125 patients in the past four years and plan to extend EECP as a community-based service. EECP has reduced readmission rates and days spent in hospital by more than threefold.

EECP is equally effective in reducing angina in patients with and without left main stem disease. [42] However, early revascularisation should be advised on prognostic grounds for patients with left main stem disease.

Few patients fail to tolerate the treatment, but some have discomfort from the pressure, initial fatigue from the exercise and occasionally aggravation of low back pain.

The treatment is more easily tolerated with a stable cardiac rhythm, ideally 50 - 80 bpm. Patients with atrial fibrillation and pacing can be treated effectively, as long as the rate and irregularity are well controlled, but anticoagulation must be meticulously controlled (INR <3).

Response to treatment is disappointing in about 10% of patients. To be effective the forces of counter pulsation need to reach the myocardium, hence the need for at least one patent coronary arterial conduit,[43] a reasonably compliant peripheral circulation and the absence of peripheral oedema and for the clinician to optimise diastolic augmentation during treatment.[17]

Retreatment may be necessary in 9% of patients successfully completing therapy at one year[39] and around 22% at three years. [19] Failure to complete the full course occurs in around 15% of patients, half of these through choice and the other half through clinical events. Retreatment results for both these categories are comparable to initial treatment results.[39]

The goals of treatment should be realistic and individualised, and psychological assessment and support available. Patients should always have optimised secondary preventive treatment and angina medication with particular attention to controlling BP and heart rate, both at rest and during exertion.

Much of the supportive evidence for EECP comes from the IEPR and although this is an uncontrolled observational study it does represent a diverse group of patients from an actual clinical setting.

COST EFFICACY

The NHS health technology assessment programme is currently undertaking a review of cost efficacy of EECP within the UK.

Patients who are ineligible for revascularisation have a high rehospitalisation rate (1.3/patient/year), which is even higher for those with angina and LV dysfunction (2.1/patient/year).[2] EECP has been shown to reduce both emergency department visits and hospitalisation significantly[44] and to reduce the need for angina medication, including short- and long-acting nitrates and calcium channel blockers.[19]

IMPROVING ANGINA SERVICES

There is clearly a need in refractory angina, to explore and research alternative therapeutic options, as recommended in the NSF for CHD.

Provision of EECP should be considered as part of a dedicated service for patients with refractory angina. This service should ideally offer a careful diagnostic assessment and a multidisciplinary approach, including psychological support and rehabilitation and in those with a continuing burden of symptoms the freedom to choose between a psychological approach with CBT, a therapeutic approach with EECP and palliative treatments that can be offered by pain specialists.

There is an increasing understanding of the role of vascular endothelium in repair and maintenance of vascular health and regulation of vasomotor tone and a growing interest in how chemical and biomechanical forces, especially shear stress may regulate both biochemically and through gene expression these vital circulatory functions.[45] Physical treatments, which act by increasing and modulating shear stress, not only in the coronary circulation but throughout the circulation may have a beneficial role in patients with diseased circulation, especially those that are unable to undertake adequate exercise as exemplified by those with both refractory angina and left ventricular impairment.

It remains to be seen whether such treatment should be considered preventively at an early stage, rather than as a last resort towards the end stage of coronary disease.

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