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Current Use of Enhanced External Counterpulsation and Patient Selection

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Summary: Most patients who receive enhanced external counterpulsation (EECP) have symptomatic coronary artery disease. These patients have either responded poorly to pharmacologic therapy or are poor candidates for revascularization procedures. Such patients receive a variety of consistent benefits from EECP treatment. As more is learned about EECP, patients once excluded from early clinical trials are now able to take advantage of EECP. Nevertheless, EECP is not suitable for some patients. It has a favorable adverse event profile for most patients undergoing the treatment. Medicare reimbursement coverage limitations remain an obstacle to having a broad cross-section of patients benefit from EECP.

Key words: angina pectoris, congestive heart failure, coronary artery bypass graft, coronary artery disease, enhanced external counterpulsation (EECP), International EECP Patient Registry, Medicare

Introduction

The use of enhanced external counterpulsation (EECP) has expanded beyond its earlier, initial uses. Currently, EECP is mostly used for patients who have symptomatic coronary artery disease. Such patients may be responding inadequately to medical therapy or are poor candidates for angioplasty or bypass graft surgery. Those in the latter category are a small number. In terms of risk and benefit, EECP continues to expand in its application to patients due to its noninvasive nature. It is also easy to apply and does not require the investment of a bypass surgery program and catherization suite.

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Benefits of Enhanced External Counterpulsation

Various clinical trials of EECP have demonstrated a host of benefits. It is successful in relieving most anginal pain. This benefit is in excess of the documented benefit in terms of ST-segment depression and improvement of thallium or positron emission tomography (PET) scan defects. Most patients undergoing EECP see improvement in their exercise-induced ischemia as measured by ST-segment depression, PET scan defects, or thallium defects. All of these tests show that inducible ischemia improves with EECP.

Exercise tolerance also improves and is sustained. This is one of the mysteries of EECP, particularly when improvement is sustained 6, 12, 24 months, or longer. It may be due to corresponding improvement in coronary perfusion, as evidenced by thallium and PET scans, or due to vasomotor tone, as evidenced by changes in nitric oxide, endothelin, and brachial vasoreactivity. Finally, there is also a sustained improvement in the patient's quality of life, which parallels many of these other more objective measures.

Precautions and Contraindications of Enhanced External Counterpulsation

Although the use of EECP may result in substantial clinical benefit, certain precautions should be observed. When EECP was first used, there was a great deal of caution exercised. EECP increases preload by increasing venous return. There was concern that if preload was increased in excess of the capacity to unload the heart, heart failure might be precipitated in those with LVD. In early studies, anyone with a history of heart failure or an ejection fraction < 35% was excluded from clinical studies. Since then, a substantial number of patients with ejection fractions below this value have been treated successfully with very low morbidity.[1] Patients with any evidence

of decompensation should, however, not be treated until they are again stable with the use of medical therapy. These patients will also need to be monitored very carefully for evidence of O_2 desaturation or other compromise (such as tachycardia) during treatment.

Aortic insufficiency has been another contraindication to EECP. However, patients with mild and even moderate aortic insufficiency have been treated successfully without placing them in jeopardy. Such concerns are similar to those with the use of the intra-aortic balloon pump in this population. Increasing diastolic pressures may aggravate any aortic insufficiency and increase end-diastolic pressure (EDP), causing pulmonary congestion. Patients with aortic stenosis, and mitral stenosis have, however, also been treated successfully despite concerns that increased preload could precipitate pulmonary congestion or heart failure. While EECP will not improve valvular heart disease, it may help if there is an ischemic or cardiomyopathic component.

Severe peripheral arterial disease remains, however, a contraindication to EECP. This is particularly true if the patient has sores or rest pain. Anecdotally, patients have been treated with mild-to-moderate peripheral arterial disease. After EECP, they report improvement in exercise tolerance and reduced claudication. Currently, the mechanism remains unknown and is the focus of a clinical trial.

Initial clinical trials also excluded patients with pacemakers or automatic internal cardioverter defibrillators (AICDs). They also excluded those with atrial fibrillation or frequent ectopy that interfered with timing. The effect of EECP on ectopy remains controversial. In some cases, increases are observed, perhaps because of increased atrial stretch due to increased venous return. Other cases, however, report decreases in ectopy. With the newer EECP timing protocols, patients with atrial fibrillation with a controlled ventricular response can be treated unless there is a tremendous amount of irregularity. Patients with pacemakers and ACIDs have also benefited from EECP treatment.

Severe hypertension (≥ 180/110 mmHg) remains a contraindication. Raising the diastolic pressure even higher could cause a problem. Over the course of EECP therapy, it is usual to see a decrease in blood pressure in 10% of patients. This may be due to a peripheral conditioning effect on vasomotor tone with alteration of the balance of nitric oxide and endothelin. Other listed contraindications for EECP are bleeding diathesis and pregnancy.

Changes in Endothelin/Nitric Oxide Ratio

During EECP, changes in retrograde diastolic aortic flow and cardiac output have been examined.[1] This has been done using Doppler echocardiography to look at the effect on blood flow in the descending aorta. Finger plethysmography was used to examine the diastolic/systolic ratio. Enhanced external counterpulsation caused retrograde diastolic flow and increased antegrade systolic flow (and cardiac output) in the aorta (Fig. 1). Systolic flow maximized at a diastolic/systolic unloading ratio of 1.5 and diastolic flow at a ratio of 2.0. Further increases in cuff pressure did not produce significant hemodynamic benefit. Therefore, a ratio of 1.5 to 2 is optimal for maximizing the hemodynamic effects of EECP. It remains unknown whether this translates into increased clinical benefit or whether a lower ratio would have the same effect. Available evidence does suggest, however, that higher ratios are associated with greater clinical benefit.

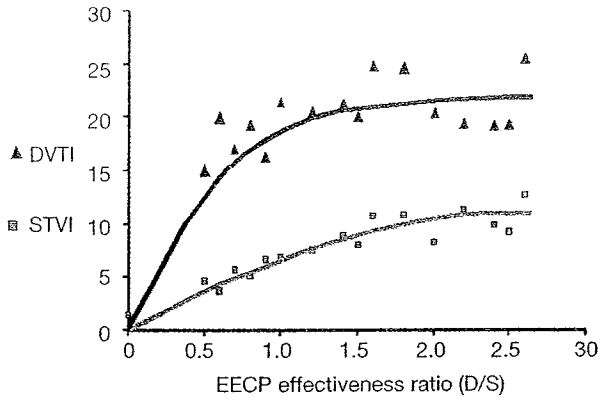

FIG. 1 Changes in retrograde diastolic aortic flow and cardiac output during EECP. DTVI = diastolic time velocity integral, STVI = systolic time velocity integral. Adapted from Ref. No. 1 with permission.

As was stated earlier, there is evidence to suggest that EECP has effects on lipid peroxidation, the renin-angiotensin system, and on the endothelin/nitric oxide ratio in terms of vasomotor tone. This effect relates, in part, to treatment duration. Over a course of treatment (36 h), the endothelin/nitric oxide ratio continues to decline (Fig. 2).[2] It is not known whether continued treatment (beyond 36 h) would produce a further decrease in the ratio or extend the durability of the effect.

Patient Selection

Patients with more severe disease, particularly in terms of their functional angina class, have greater potential for improving after undergoing EECP. Various independent predictors of improvement in angina class after EECP have been identified (Table I).[3,4] Patients who are unable to complete the treatment are much less likely to benefit from it. Various conditions, such as diabetes, also correlate with reduced effectiveness. When patients with diabetes are treated with EECP, they already have established vascular disease. Whether or not the dosing should be adjusted is one of the areas of controversy.

Effectiveness of Enhanced External Counterpulsation

In our early studies, the majority of patients (78%) undergoing EECP showed improvement as demonstrated by thallium perfusion.[5] There were 22% who did not respond at all. Approximately two-thirds of patients had resolution of their

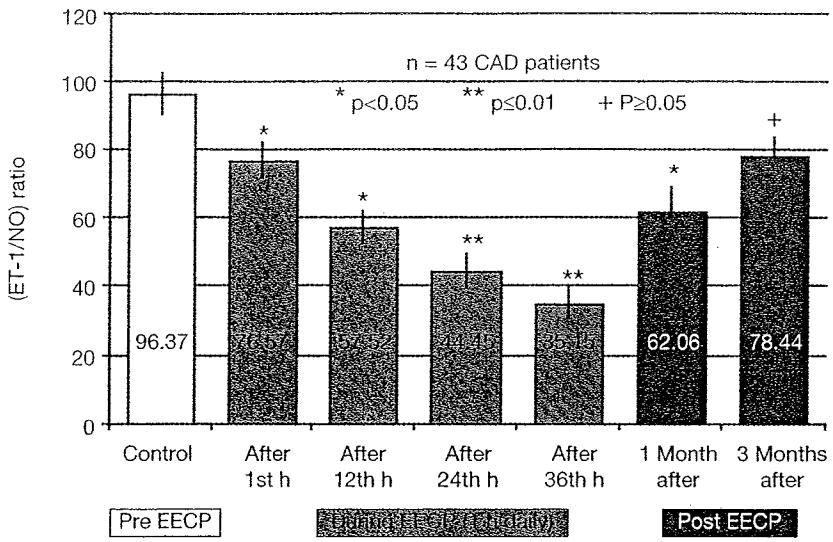

FIG. 2 Changes in plasma endothelin/nitric oxide (ET-NO) ratio before, during, and after EECP. Adapted from Ref. No. 2 with permission.

ischemic defects in these early studies. Also, approximately three-quarters of patients improved at least one angina class, with some improving as much as three classes.[6]

Some subsets of patients were studied to investigate the open artery hypothesis. According to this hypothesis, a patent artery is needed proximally in order to transmit the increased pressure and volume to the distal circulation. It remained unclear, however, whether this opened collaterals, recruited new collaterals, or just developed the sheer stress distally that would enhance the development of angiogenesis and form new collaterals.

When patients with single-, double-, and triple-vessel disease were examined, a difference was noted in terms of response for those patients with one- and two-vessel disease (Fig. 3).[7] More extensive disease responded less well. This supported the idea that an artery needed to be open in order to transmit the pressure. Another explanation was that simply more extensive disease did not respond as well to EECP treatment, at least within the usual 35 h of treatment.

The relationship between EECP effectiveness and coronary artery bypass surgery has also been studied.[8] The premise was that patients with more conduits tended to respond better than those who did not have these extra conduits. Patients with more extensive disease, such as those with triple-vessel disease, did not do quite as well as those with single- and double-vessel disease (Fig. 4). A substantial number, however, did respond to therapy.

The length of treatment, specifically 35 h, came from the Chinese experience. At the time the United States imported EECP, Chinese researchers were treating patients for 36 h.

TABLE I Independent predictors of improvement in angina class after EECP treatment.

Variable	Odds ratio
CCS class II	2.17
CCS class III	5.29
CCS class IV	6.69
Treatment hours	3.47
Diabetes mellitus	0.67
History of CHF	0.81
Prior CABG	0.76

Abbreviations: CCS = Canadian Cardiovascular Society, CHF = congestive heart failure, CABG = coronary artery bypass graft. Reprinted from Ref. No. 4 with permission.

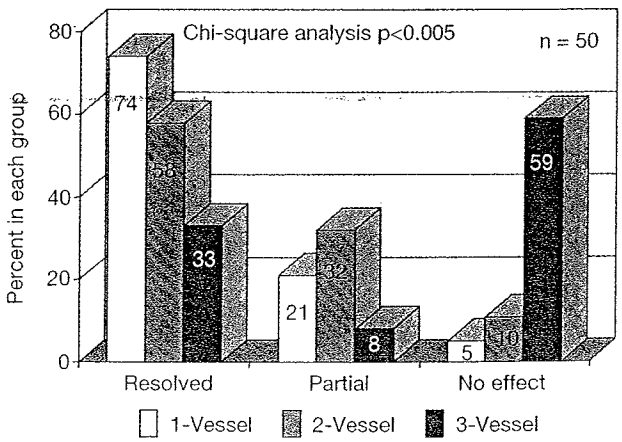

FIG. 3 Impact of residual coronary artery disease on post-EECP changes as measured by stress radionuclide perfusion testing. Reprinted from Ref. No. 7 with permission.

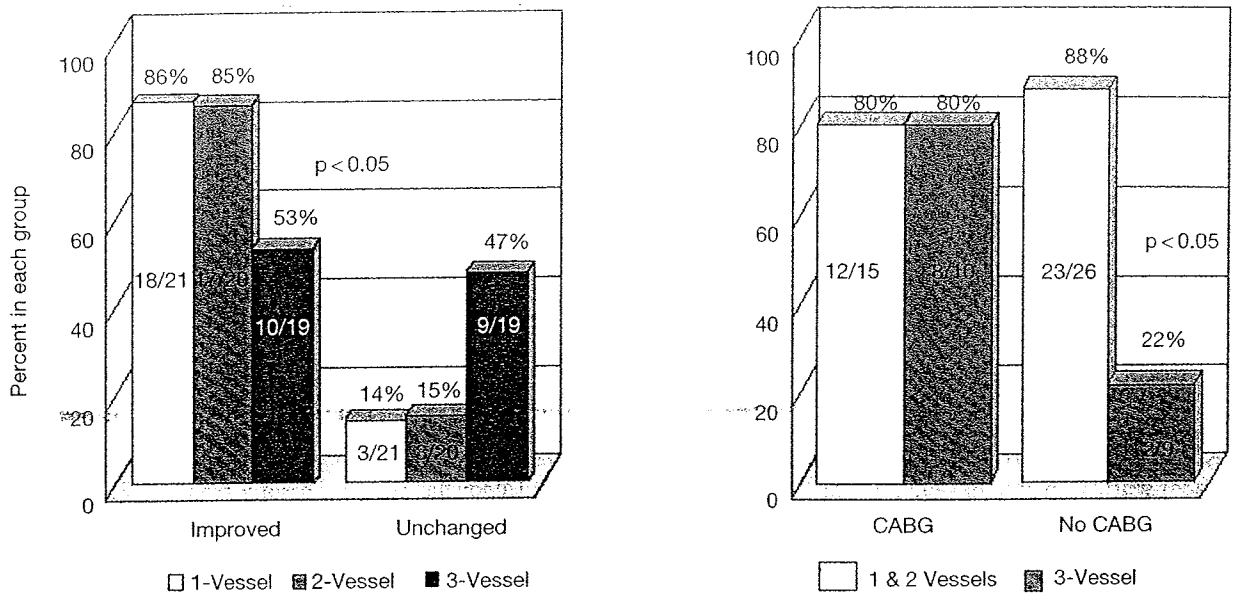

FIG. 4 Impact of coronary artery bypass graft on the benefit of EECP with one-, two-, and three-vessel disease (n = 60). Reprinted from Ref. No. 8 with permission.

During treatment, they performed serial stress tests every 12 h. Some patients were found to improve after 12 h, while more improved after 24 h.[9] By 36 h, the effect of EECP had reached a plateau (Fig. 5). Follow-up showed the effect to be sustained and somewhat better even after 6 months. In the U.S., early trials also used the 36-h dosing schedule. Unlike the Chinese, who work 6 days a week, Americans only work 5 days. To accommodate this custom, EECP was cut back to 35 h over 7 weeks.

The International EECP Patient Registry (IEPR) tends to confirm many of these data in terms of early, smaller trials.[1] Most patients upon entry into the IEPR were classified into functional classes II to IV. After treatment, the majority of patients moved into classes I and II, with some patients experiencing no angina. The effect persisted immediately post study and after 1 year.

Compared with invasive techniques available, adverse events are really quite limited, according to initial IEPR registry results. These include skin and musculoskeletal problems as well as unstable angina. Cardiac adverse events seem to rise slightly as EECP is extended to the treatment of patients who are more ill with congestive heart failure (CHF) (Table II).[1] Currently, the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) trial is comparing the occurrence of these events in patients with CHF who do and do not receive EECP treatment.

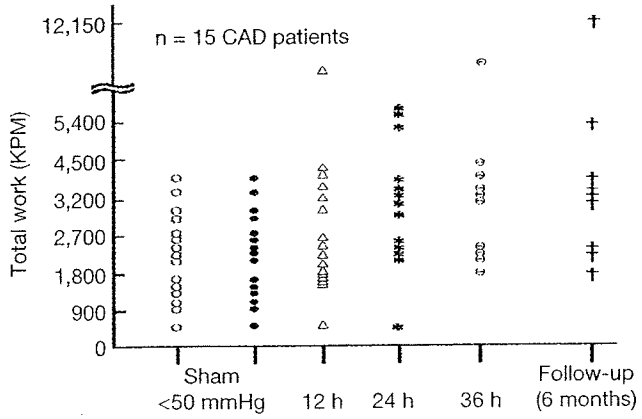

FIG. 5 Measurement of multiple exercise stress test after various doses of EECP and follow-up at six months (n = 15). CAD = coronary artery disease, Sham = cuff pressure less than 50 mmHg. Adapted from Ref. No. 9 with permission.

TABLE II Cardiac events in 6 months following EECP in patients with and without history of congestive heart failure from the International EECP Patient Registry.

Percentage with events	No CHF (1,409)	CHF (548)
Unstable angina	7.4	9.0
MI	2.5	3.6
CHF	2.4	7.2
CABG/PCI	4.9	3.6
Cardiac Hosp	13.6	19.1
Death	2.2	7.9
MACE	8.6	14.4

Abbreviations: CHF = congestive heart failure, MI = myocardial infarction, CABG/PCI = coronary artery bypass graft/percutaneous coronary intervention, MACE = major adverse clinical event. Adapted from Ref. No. 1 with permission.

Conclusion

Who gets EECP treatment in the U.S. is driven, in large part, by Medicare reimbursement policies. According to Medicare, patients are only covered for the EECP procedure if they have angina refractory to medical therapy and are not candidates for revascularization with angioplasty or bypass surgery (due to excessive procedural risk, limited targets, chronic total occlusion, comorbidity).

Given the rapid developments of EECP over the past few years, where will it be in another 5 years? It is hoped that EECP will be prioritized for use higher than its current position behind medicine and revascularization.[11] The desire is for EECP to be considered a treatment option when a patient does not respond to medication but before revascularization. Future indications will also expand to include a broader patient base (Table III). Enhanced external counterpulsation is a very widely applicable treatment, as evidenced by the successful treatment of patients enrolled in the IEPR who are ≥ 100 years old. In the future, it is expected that more patients will benefit from this innovational treatment for angina and other cardiovascular conditions.

TABLE III Future indications for EECP

- CAD patients with inadequate response to medical therapy
- Treatment of MI (acutely, to prevent adverse remodeling and to promote functional recovery)
- Treatment of ischemic and ? nonischemic cardiomyopathy
- Secondary and ? primary prevention of vascular disease progression

Abbreviations as in Table II. Reprinted with permission of Dr. Lawson.

Discussion

Participant: Does the American College of Cardiology have any position or a position paper on EECP therapy?

DeMaria: I don't think the ACC has written a position paper on EECP that I have seen. There may be one underway.

Beller: I can't speak for the guideline group on stable angina, but I think some of these studies, such as the MUST EECP came out after the stable angina guidelines. EECP might be mentioned in the text but there is no mention of a class I/class III indication because it is so early in the game.

Conti: We have talked about it in EXCEL, the audio journal of the American College of Cardiology. In addition, Kim Eagle has published some material in his Current Journal Review. The CJR has got something relating to this, and also comparing it to spinal cord stimulation, transmyocardial rate of revascularization, but no hard data, just a lot of editorial commentary.

Participant: We asked our EECP patients directly about their ability to perform sexually. Has there been any work conducted in this area of interest?

Lawson: There has been a preliminary report of EECP as benefiting patients with erectile dysfunction.[12] The IEPR is actually doing a substudy to look at the benefit of EECP in patients with erectile dysfunction, as well as to look at proteinuria in diabetics, which may reflect diffuse endovascular dysfunction diffusely. So those are topics of interest that are being pursued.

Participant: Currently, the EECP device is not portable. Is the issue of portability going to be addressed in the future, and how does one determine where to place it in the institution?

Conti: One of the issues you have, though, with this device—Dave has his in his cath lab. Most of us have it in a room someplace, and although this device is movable if you have a moving van, it is not mobile. I mean, it is not something you can push down the hall unless there are devices now that are coming along that would...I assume there will be devices that are going to be mobile. That is when we will be able to use it in cardiogenic shock and I think there is a use for it in that particular situation.

Holmes: We have the opportunity to use it in folks with unstable angina in that our office is attached to the hospital, but we have to discharge them from the hospital first. They are discharged, have their first treatment on the way out. We run them back and forth. Many of them are not readmitted. And those that are, we discharge them within hours for their next treatment and run them back and forth, and we have done this with four people so far that were intractable and kept them from having to go on to further procedures. Well, all of them had no procedures available, but our proximity really helped this, and I think the University of Pittsburgh has it in the hospital and treating people in the hospital.

Conti: Well, we have ours in the hospital too, but it is in the outpatient clinic section of the hospital. It is just not convenient to take patients up there who are sick. I prefer to be in the cath lab or some other place in the coronary care unit, but we only have one unit so we can't move it around.

DeMaria: One of the downsides that we haven't alluded to yet, I suppose we should own up to is that this is not the quietist device the world has ever seen and we have it in our heart station. It used to be next to the room where we interpreted echocardiograms and after a week we moved it down the hall a little bit, and after 2 weeks we moved it even further down the hall.

Participant: Well, we solved that problem by using carpets and insulated the walls. We actually have it also next to the cath lab and next to physician rooms and it doesn't really interfere with our daily work.

Participant: For patients who are denied EECP therapy by third-party payers, do you have any suggestions as to how we might convince them that this is not "experimental" as they are prone to say?

DeMaria: Medicare reimburses for this procedure. In my state of Florida, Medicaid is pretty poor. It is a tough problem if you don't have the insurance to pay for it. But I suspect Blue Cross and Blue Shield will pay for it in some situations.

Participant: In California, they only pay for it if the physician is in the room for the treatment, and that is not typically the case in most institutions.

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