REJUVAHEART™

In the United States, one out of every 2.9 deaths is related to cardiovascular disease[1]. Coronary Artery Disease (CAD) is the single leading cause of death in America today and the American Heart Association (AHA) estimates the cost and prevalence of heart disease to triple to over $800 billion/year by 2030. The AHA is calling on more aggressive preventive approaches to contain this skyrocketing problem. That approach is now easily available with RejuvaHeart.

With these staggering numbers, having treatment options becomes invaluable to ensure patient compliance and outcome success. External Counterpulsation has demonstrated a number of positive effects that are maintained for at least three years after a full course of treatment.

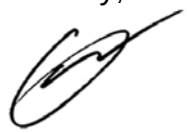
North American Heart Institute (NAHI) is dedicated to expanding provider and public knowledge about this treatment modality by offering dedicated centers and targeted marketing to increase public awareness and interest. We call it the RejuvaHeart™ program.

We are delighted in your interest in becoming a Provider in the RejuvaHeart network of physicians. We offer a number of benefits including access to clinical specialists for chart review, direct to consumer advertising to increase patient awareness and volume as well as constant service and support. We have taken every precaution to ensure the success of our program including extensive research into the operation of this program type within your state.

With your extensive knowledge and clinical expertise, we feel that you would be an invaluable asset to our network and that our affiliation can help build your practice in multiple ways.

If you have any questions about the attached information, please call us to discuss. Participation in our network offers many benefits to you and your patients with no obligation and no risk. We look forward to a long and prosperous relationship.

Sincerely,



Carlos Becerra, CEO
North American Heart Institute
www.northamericanheart.com

[1] American Heart Association Cardiovascular Disease Statistics Alert, www.americanheart.org/2006

North American Heart Institute

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WHAT IS ECP?

For people with angina or heart failure, even simple activities—such as going to the mailbox or walking the dog—can be challenging.

If you are one of these people, take heart. There is a non-invasive treatment called RejuvaHeart™ External Counter Pulsation. This therapy has clinical experience that has shown to be safe and beneficial for the treatment of angina and heart failure. Approximately 80% of patients who complete the 35-hour course of RejuvaHeart™ therapy experience significant symptom relief that may last up to three years.

HOW DOES IT WORK?

RejuvaHeart™ therapy is an outpatient treatment that is usually given for an hour once or twice a day, five days a week, for a total of 35 hours. During the treatment, you lie on a comfortable treatment table with large blood pressure-like cuffs wrapped around your legs and buttocks. These cuffs inflate and deflate at specific times between your heartbeats. A continuous electro cardiogram (ECG) is used to set the timing so the cuffs inflate while the heart is at rest, when it normally gets its supply of blood and oxygen. The cuffs deflate at the end of that rest period, just before the next heartbeat. The special sensor applied to your finger checks the oxygen level in your blood and monitors the pressure waves created by the cuff inflations and deflations. Basically, the RejuvaHeart™ Therapy External Counter Pulsation system pumps when your heart is resting and releases when your heart is working.

WHAT DOES THIS MEAN?

Well, it means that your heart is getting increased oxygen and blood flow without having to work as hard. External Counter Pulsation (ECP) can decrease the need for medication and reduce or eliminate the frequency and intensity of chest pain. It can also improve your ability to participate in activities of daily living. External Counter Pulsation (ECP) is also believed to create new pathways around blocked arteries in the heart by expanding or growing what are called collaterals, additional networks of tiny blood vessels that supply the heart muscle. After completing treatment, many patients are able to enjoy moderate levels of exercise for the first time since the onset of their angina symptoms.

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REJUVAHEART™ REVENUE

You treat the patients, we handle the rest.

The RejuvaHeart program opens the door to new revenue opportunities while addressing today's demanding clinical environment.

INSURANCE REIMBURSEMENT

Medicare approved the reimbursement for this therapy as a standard treatment option in July of 1999. The comprehensive standard procedure code in use today (G0166) was assigned in January of 2000.

Since the procedure was identified in the Comprehensive Procedure Terminology (CPT) manual, most HMO's and insurance companies adopted the code as industry standard.

USUAL, CUSTOMARY, AND REASONABLE

The average reimbursement amount for ECP under Medicare guidelines is from $140-160 per session based on your contract and regional fee schedule. A full course of therapy usually consists of 35 one-hour treatments.

With only 20 patients, you can increase your practice income by $100,000 annually.

DOCUMENTATION

The RejuvaHeart system integrates intelligent features to make operation easy and automatic.

- RejuvaHeart system workflow and screen layouts are intuitive and easy to navigate, even for inexperienced clinicians.
- Administrative and Clinical records are maintained in the device and can easily be integrated into EMR or patient file charts.
- Automatic Peak-to-Peak Ration Calculation – Eliminates manual task previously done up to six times per hour.
- Database backup utility can easily save one or more selected patients to a single CD, USB device, or network server to protect against a hard drive crash.

REJUVAHEART SUPPORT

- ✓ Equipment, Installation and Service
- ✓ Extensive training for provider and staff
- ✓ Unlimited Clinical Support
- ✓ Online device diagnostics
- ✓ Access to RejuvaHeart Cardiac Network
- ✓ Marketing to patients and providers
- ✓ Public Relations

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REJUVAHEART™ ADVANTAGE

You treat the patients, we handle the rest.

The RejuvaHeart ECP system opens the door to new revenue opportunities while addressing today's demanding clinical environment. The system is designed to deliver effective therapy and seamlessly integrate with information technology systems, track patient outcomes and improve efficiency for clinicians.

Dependable ECP Therapy
RejuvaHeart ECP systems incorporate advanced technology with proven effectiveness and reliability, based on over one thousand systems installed and 11 years of experience. RejuvaHeart systems incorporate the latest ECP innovation of vacuum-assisted deflation. Benefits include:

- Longer hold time for fast heart rates – Faster deflation allow more time for inflation hold time. This is especially important for faster heart rates where hold time is very short.
- Fastest systolic unloading and minimized "slamming" – It is critical that the ECP system unload the heart during systole. When a premature beat triggers an early deflation, vacuum-assist pulls out the air fast to release pressure before systole. Then when the system inflates early following the early beat, residual air can cause "slamming". Since vacuum-assisted deflation minimizes residual air, it minimizes "slamming".
- Most complete deflation – Vacuum-assist completely deflates bladders and completely relaxes cuffs to allow free flow of blood back to the legs and feet. Incomplete deflation can hamper blood flow and even lead to "tingling" in the feet. Patients can feel the difference.

Unmatched Productivity and Ease of Use
Intelligent features make operation easy and automatic.

- RejuvaHeart system workflow and screen layouts are intuitive and easy to navigate, even for inexperienced clinicians.
- Automatic Peak-to-Peak Ration Calculation – Eliminates manual task previously done up to six times per hour.
- Database backup utility can easily save one or more selected patients to a single CD, USB device, or network server to protect against a hard drive crash.

Integrated Outcomes
Tracks and reports on individual patient and group Outcomes including excusive integrated quality of life survey to track patient progress including SF-36 and Minnesota Living with Heart Failure

Regulatory Compliance
US FDA 510(k) clearance for marketing
System is safety certified to the UL 60601 standard.

Comprehensive Information Technology Solutions
Integrates with information systems through a seamless interface. RejuvaHeart systems offer assistance via remote software clinical and technical support from service headquarters.
Log into the system via internet connection

- View system screen remotely
- Operate system remotely
- Download files to Support Center
- Upload software patches and data to customer

Clinical training
Full three days of clinical training provided by an ACLS certified RN with extensive clinical experience. We provide unlimited clinical support and evaluation of strips for the life of the system.

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PRODUCT SPECIFICATIONS

You treat the patients, we handle the rest.

Treatment Pressure Range
- 0 – 6 PSI/310 mmHg

Treatment Duration Timer
- 10-60 minutes; 5 minute increments
- Treatment and air/vacuum pump stop when set time expires

Treatment Cuffs
- Durable & cleanable high denier Nylon with Velcro closure
- 3 sizes fit all patient types
- Buttock and thigh cuffs are separate for better fit

Table
- Motorized, continuously adjustable backrest
- 0 to 45 degrees
- Safe Working Load: t 350 lbs. /160 kg
- Easy to clean, fluid resistant fabric
- Quick connect hoses attach without tools

System Protection
- Bed Base ON/OFF switch is fused
- Air/Vacuum Pump relay is overload protected
- Air/Vacuum Pump is thermally protected

Printer
- Wireless, Laser*

Patient Care Package
- Initial supply of electrodes, treatment pants, cuffs and bladders

Patient Protection
- Automatic vacuum deflation of cuffs on early / extra systole
- Over pressure limit protection
- Treatment is suspended during episodes of high or low heart rate
- Emergency stop button
- Auditory alarms:
  - Heart rate out of limits– Oxygen saturation out of limits*
  - Lack of an adequate triggering signal
  - Loss of communication between computer and ECP device
- Air to cuffs is actively cooled, always below body temperature

Equipment Dimensions and Weight
Pole Cart: Wheel base 29”/74 cm
Height: 66” (168 cm)
Weight: 35 lbs.(16 kg)
Bed Base: Width 29.25” (75 cm)
Depth 67”(170 cm) max./52” (132 cm) min.
Height 28.5” (72 cm)
Weight: 350 lbs. (159 kg)
Removable Mattress: Width 34” (86 cm)
Depth 82” (208) cm
Height 5” (13) cm

Power Requirements
- 1 – 110 VAC 60Hz 15 A standard or hospital grade outlet
- 1 – 220 VAC 60Hz 20 A dedicated, twist and lock outlet
- 220VAC 50Hz compatibility upon request

International Specifications:
- Standard 220vac 10 amp (min) outlet
- 1-Dedicated 220vac 15amp outlet (NEMA L6-20R)

Operating Environment
- Temperature 65-75ºF/18-24º C
- Air conditioning capacity: at least 8800 BTU per hour
- Relative Humidity 35-65%
- Absence of electromagnetic interference in the area (e.g.: MRI device)
- Free of flammable anesthetics

Please call for additional information

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RejuvaHeart™

ECP Market Opportunity

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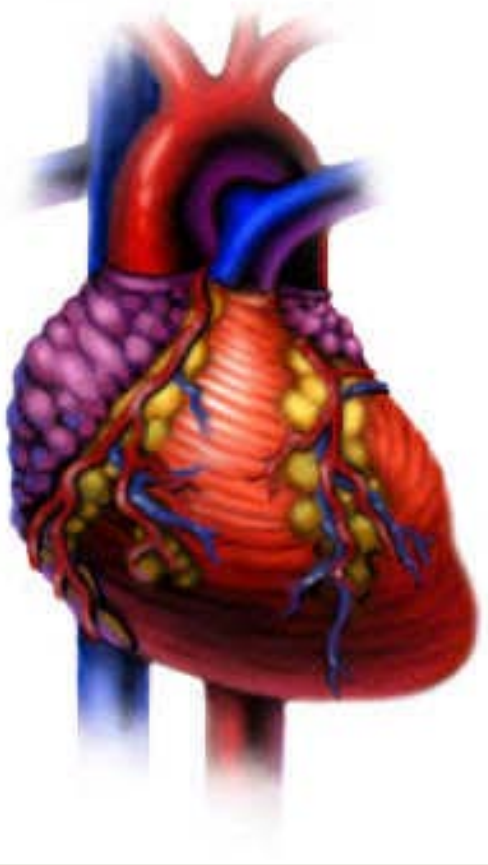
RejuvaHeart™

Cardiovascular Disease is America's #1 killer

10.2 Million Americans suffer from Angina*

- **2010 direct and indirect cost in treating CVD estimated to be $503.2 billion***
  - Coronary Heart Disease is projected to be $316.4 billion*
  - $47.4 billion paid to Medicare beneficiaries in 2009**
  - 1 in 3 Americans (36.9 percent) have some form of heart disease*



American Heart Association Cardiovascular Disease Statistics*
Center for Medicare and Medicaid Services annual expenditure report CVD**

Heart Disease Prevalence

About 70 million Americans have one or more types of cardiovascular disease (CVD)

- High blood pressure (HBP) — 65 million
- Coronary heart disease — 13 million
  - Myocardial infarction (heart attack) — 7 million
  - Angina pectoris (chest pain) — 6 million**
- Congestive Heart Failure — 5 million**
- Stroke — 5 million
- Congenital CV Defects — 1 million

**** ECP Patient Treatment Opportunities**

Note: Numbers add to >70 million because a single patient may have more than one condition.

Angina Pectoris

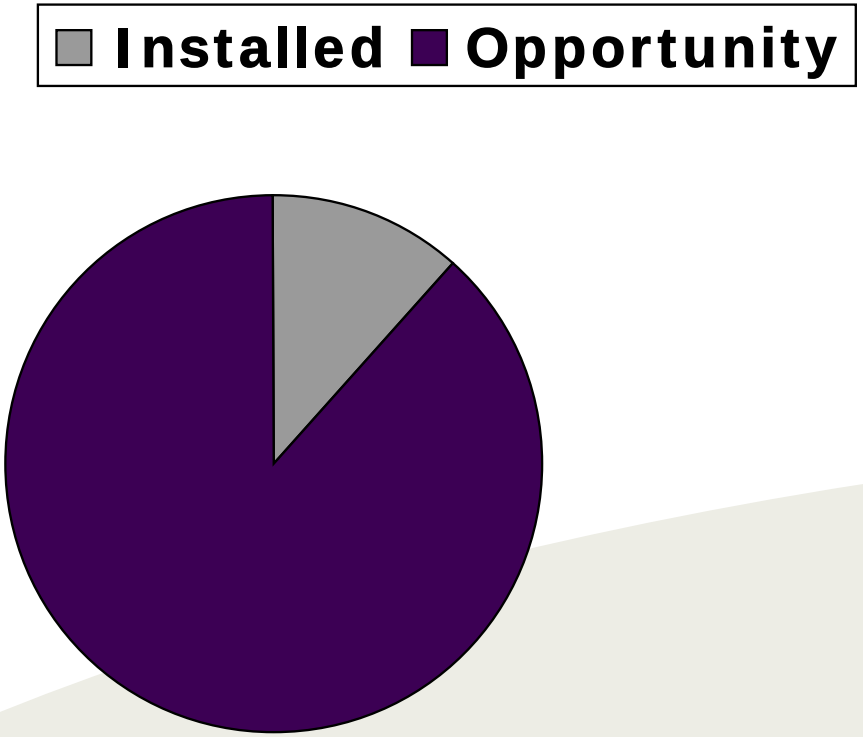
Chest pain or discomfort due to insufficient blood flow to the heart muscle (ICD/9 413 and ICD/9 120)

- **Stable angina is predictable chest pain on exertion or under mental or emotional stress**
- **Medicare reimburses ECP for patients with refractory stable angina**
  - Refractory means not treatable any other way

RejuvaHeart™

ECP Opportunity with Angina

- Over 450,000 new patients per year meet Medicare reimbursement criteria
- 13,000 ECP systems required (@35 patients/unit)
- Only about 1500 ECP systems installed to date



Only 12% of needed systems have been sold so far!

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Congestive Heart Failure

Heart failure that results in retaining excessive fluid, often leading to swelling of the legs and ankles and congestion in the lungs (ICD/9 428.0 ICD/10 150.0)

- **5 million Americans have CHF with 550,000 new cases presented each year**
- **75% of people under age 65 who have CHF will die within 8 years**
- **CHF drains hospital profits - $28 billion in 2005**
- **ECP cleared by FDA for CHF—CMS reimbursement hoped for in 2012**

BIG ECP Opportunity with reimbursement

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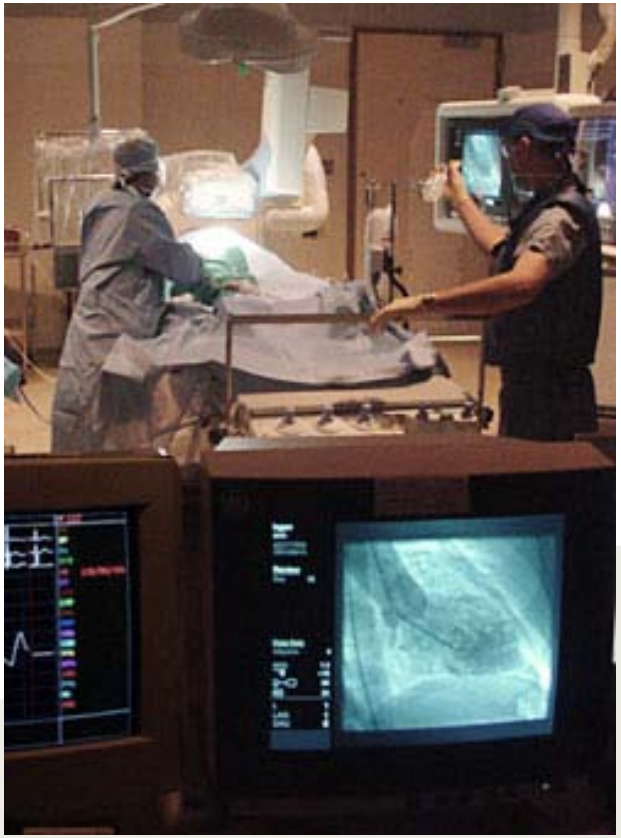
Cardiac Catheterizations

1.5 million procedures

- **At a mean charge of $17,000**



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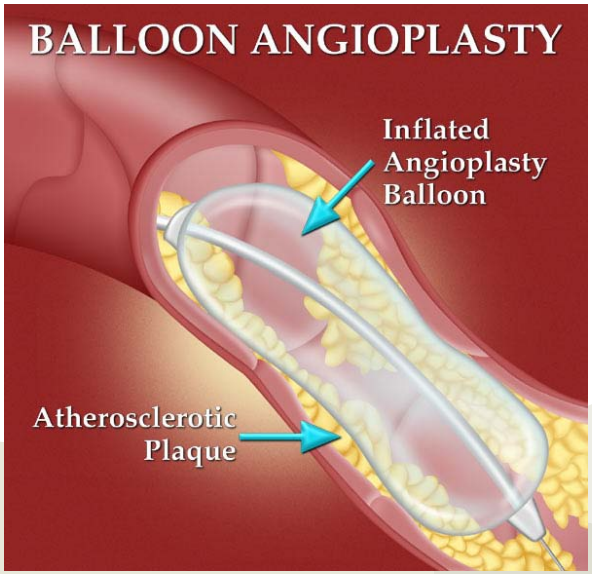
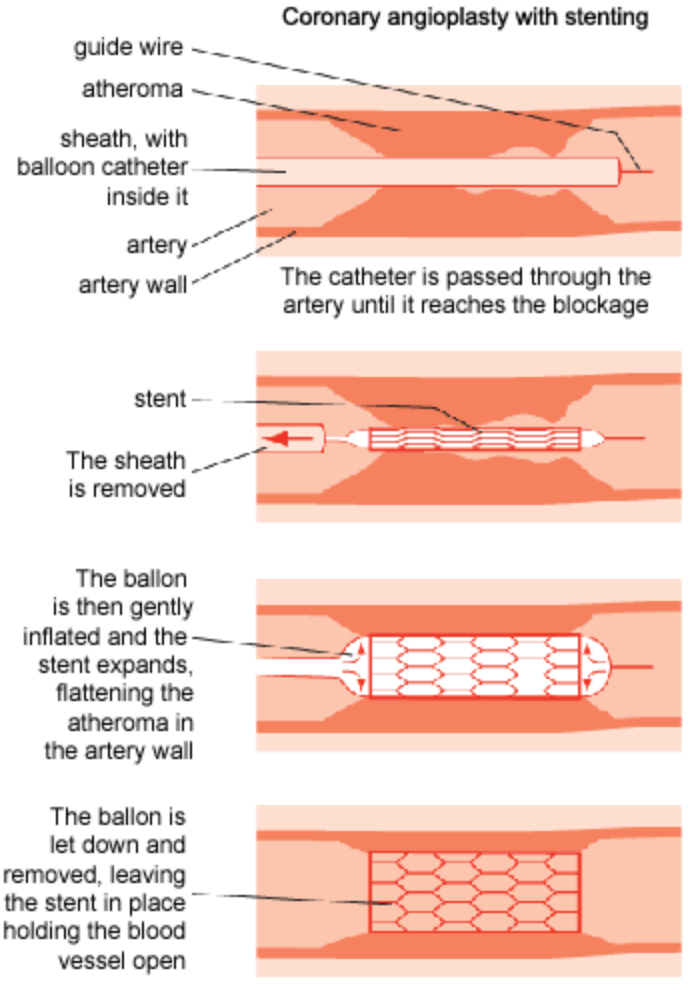
Angioplasty

PTCA—657,000 procedures

Stenting—537,000 procedures

- **At a mean charge of $29,000**





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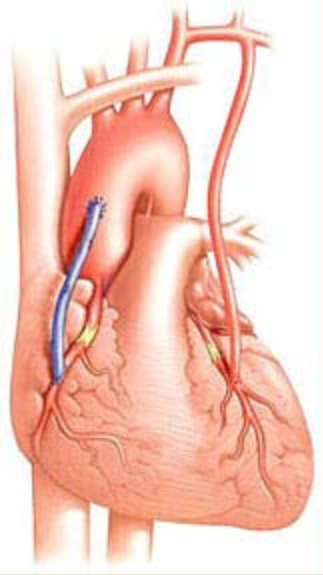
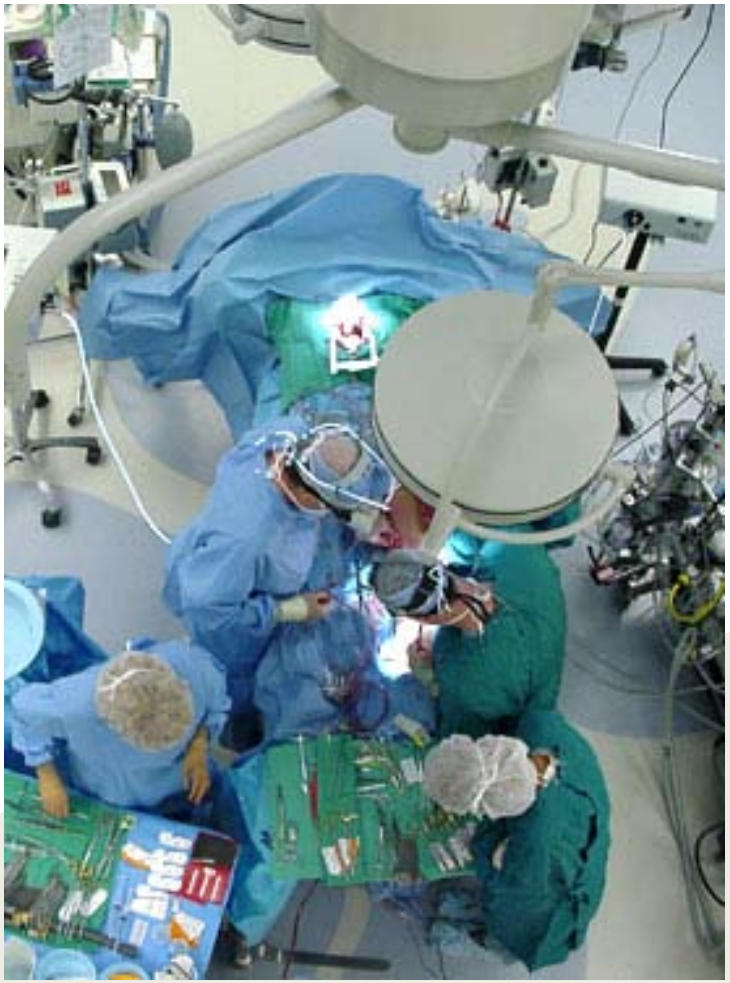
Coronary Artery Bypass

530,000 procedures

- **At a mean charge of $61,000**



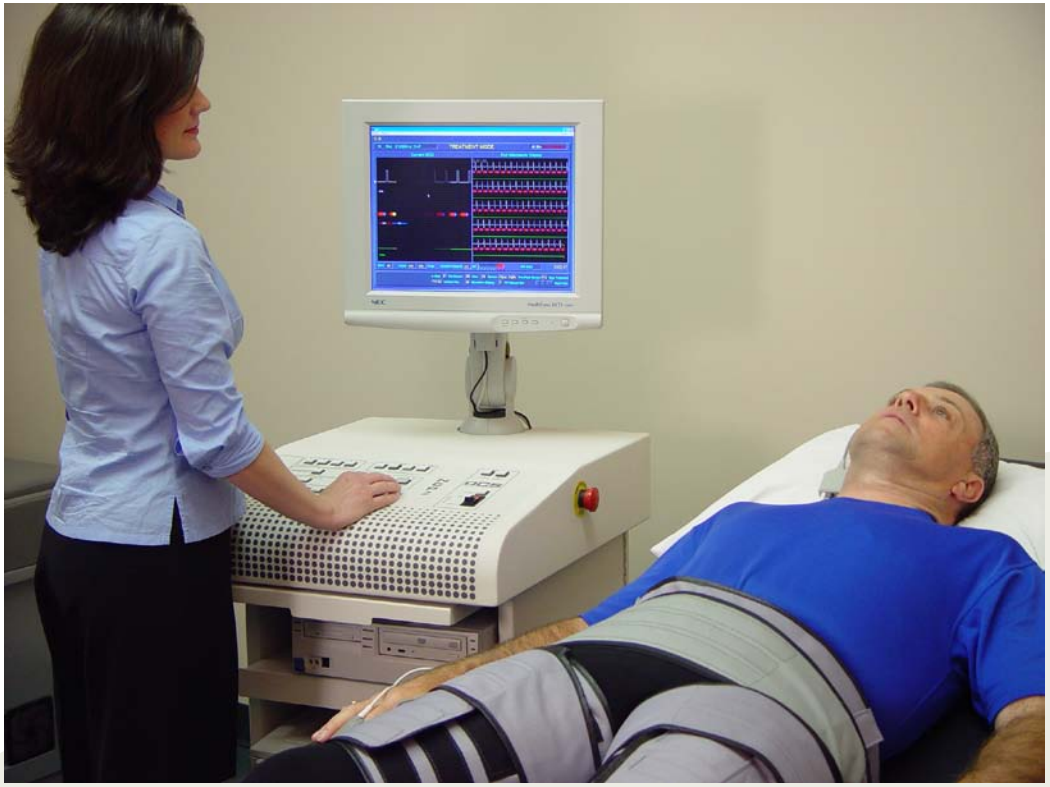


RejuvaHeart™

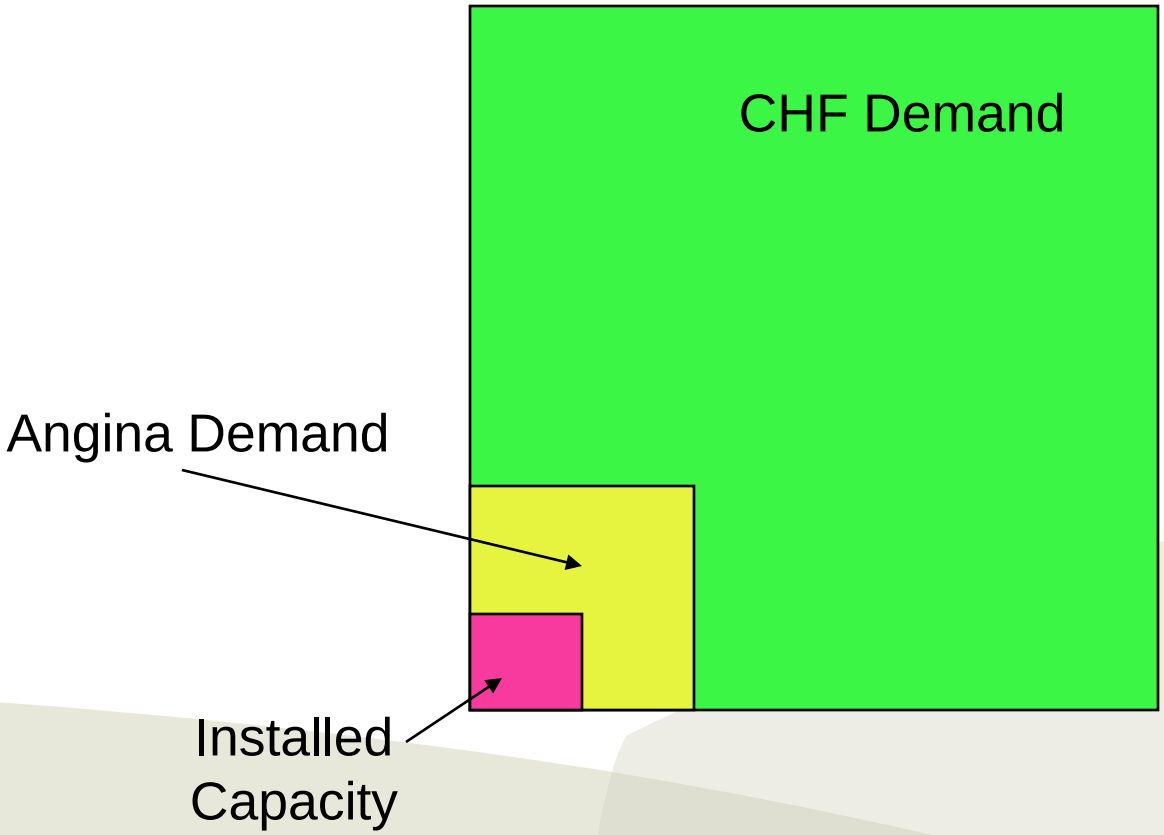
External Counterpulsation

50,000 procedures

- **At a mean charge of $4,800**



Total Potential Market for ECP



Lots of room to grow for ECP!

ECP Market Growth

It's only just begun.

ECP is...

- **Non invasive**
- **Inexpensive**
- **Market is underserved**

RejuvaHeart™

External Counterpulsation (ECP)

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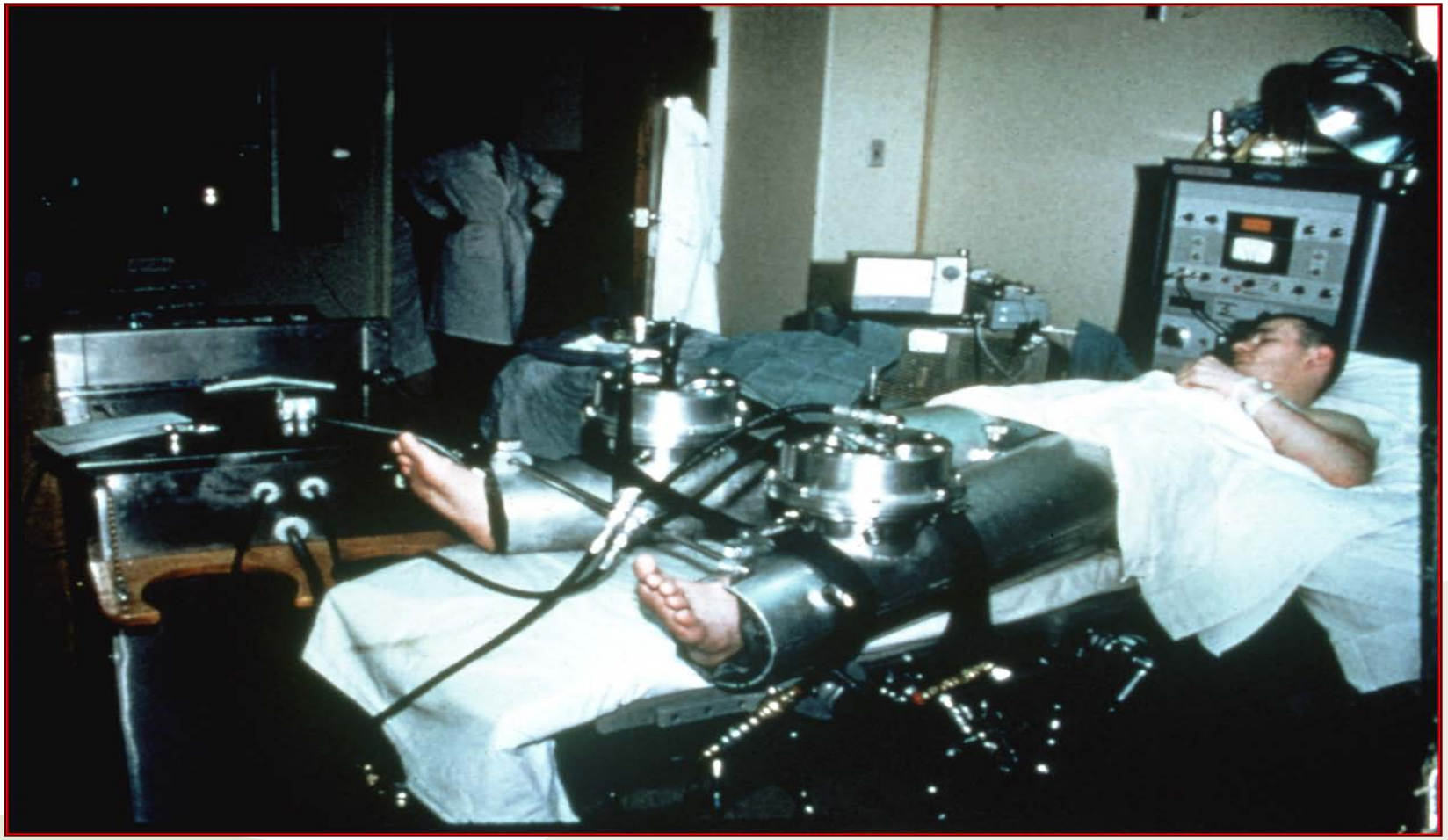
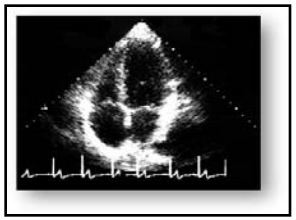


Original/Predicate ECP Device

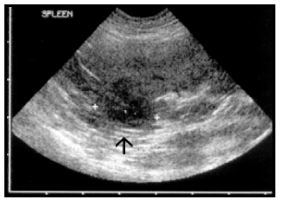
For the angina patient, the primary benefit of restored blood flow and resolution of ischemia is *relief of angina symptoms!*

Recommended Screening Tests:

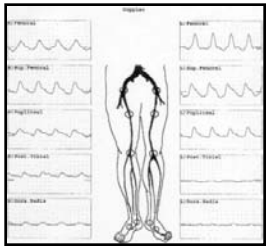
Recent Echocardiogram
(6 months to 1 yr.)



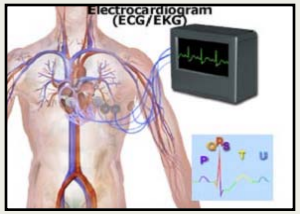
Abdominal Ultrasound



Doppler Studies



Recent EKG



Candidates for ECP

Patients with documented ischemia by non- invasive testing or angiography.

With Canadian Class III or IV angina symptoms despite medical therapy.

Who are felt not to be readily amenable to PCI or CABG.

Or considered to have increased risk for invasive intervention.

Candidates for ECP

Patients with anginal equivalent symptoms (e.g.. dyspnea, fatigue related to ischemia).

Patients with Prinzmetal's or Microvascular angina w/ CCSC III/ IV symptoms despite medical treatment.

Contraindications:

- Aortic Insufficiency
- Severe Valvular Disease
- Cardiac Catherization (< 2 weeks)
- Arrhythmia
- Presence of abdominal aortic aneurysm
- Severe Hypertension (>180/110 mmHG)

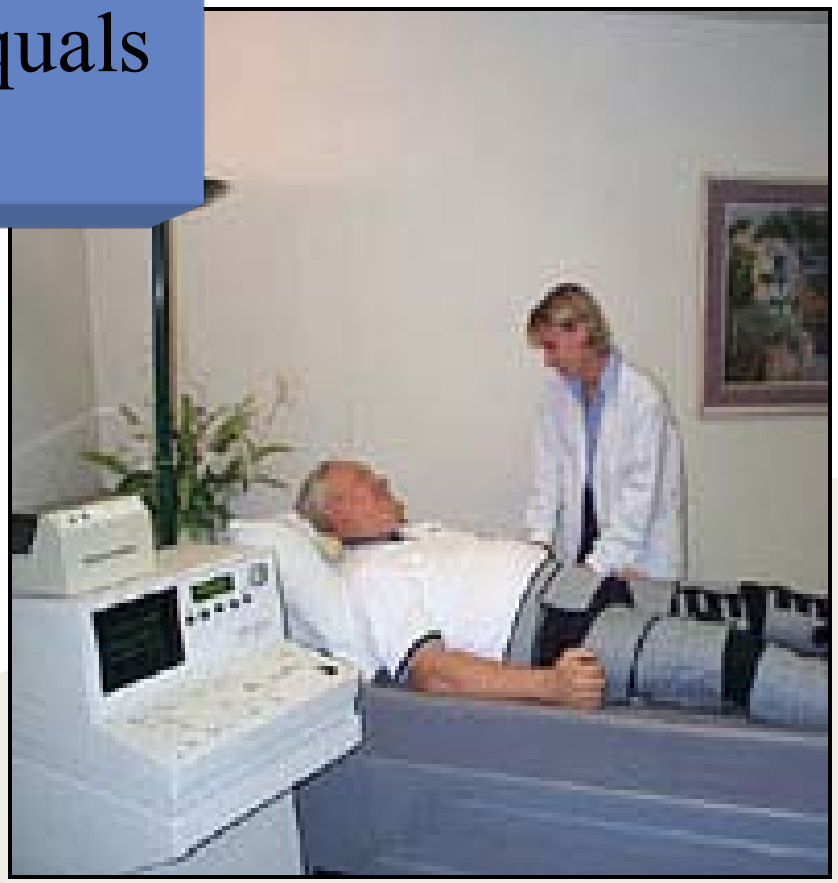
Treatment Regimen

Total course of treatment equals
35 one-hour sessions

Treatments are conducted *daily*

Five days per week

For seven weeks



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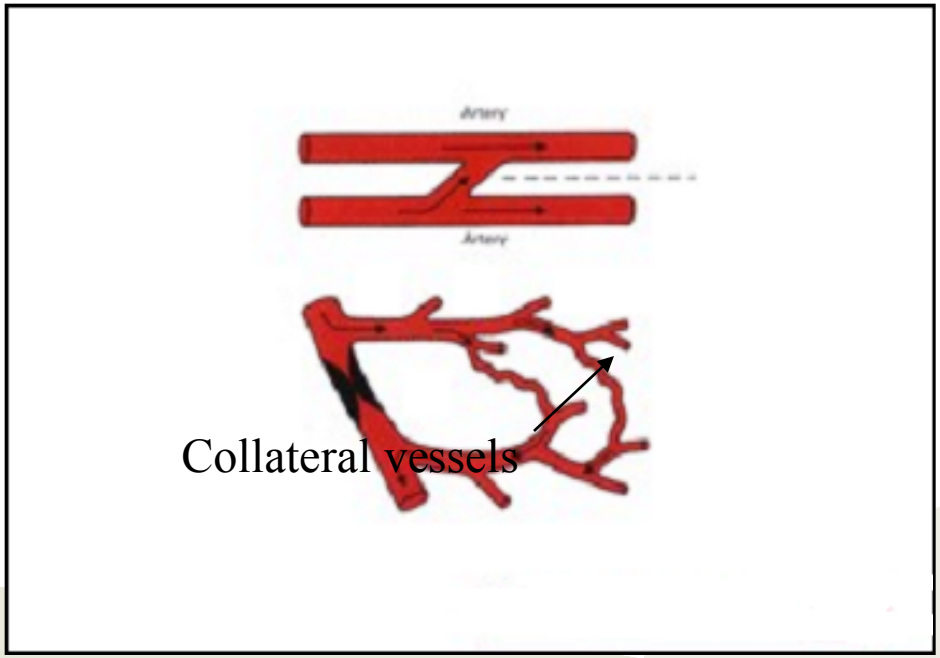
The primary mechanism by which ECP reduces/resolves myocardial perfusion defects and restores blood flow to the heart muscle is hypothesized to be the …

Stimulation of collateral vessel recruitment and/or growth

Collateral Circulation



The development of new collaterals, provides permanent conduits to the myocardial tissue previously deprived of oxygen.

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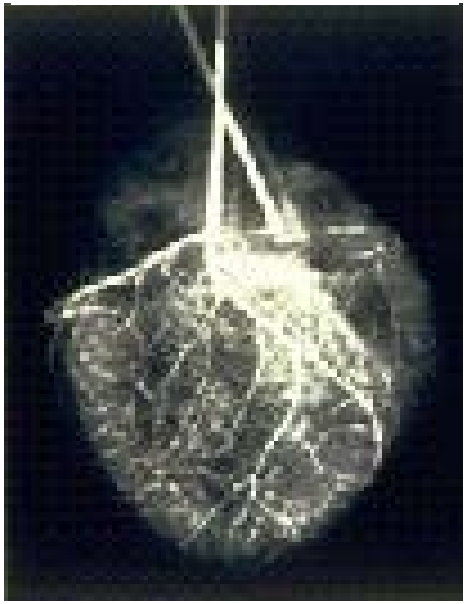
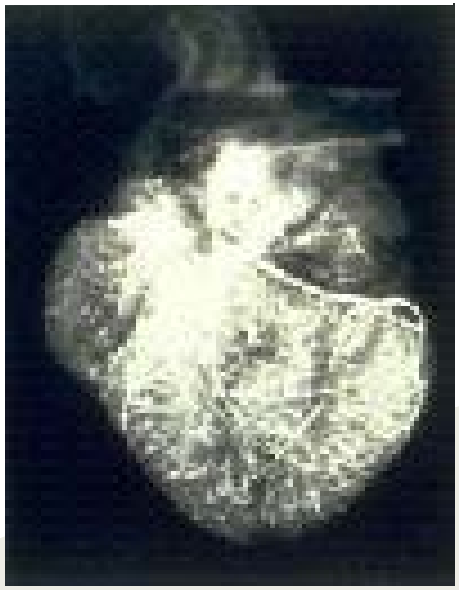
Collateral growth post-ECP treatment:

Pre- ECP



Perfusion Deficit

Post- ECP

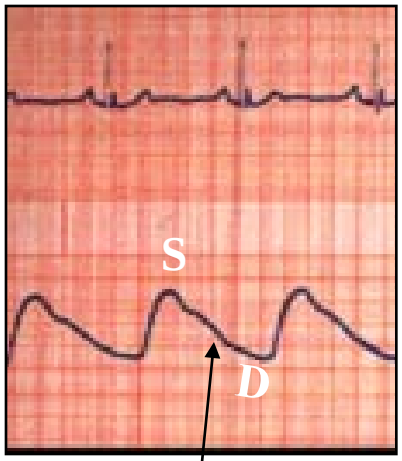


Restored blood flow

Pulse Wave: Unaugmented vs. Augmented

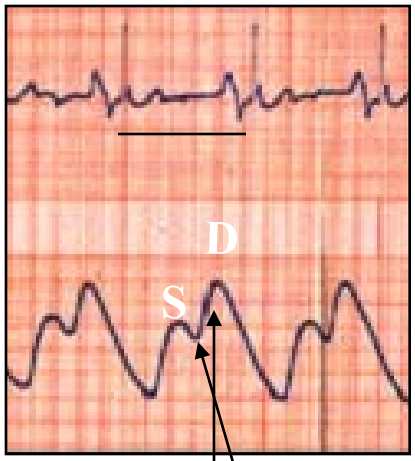
Normal systolic pressure is physiologic-ally higher then diastolic pressure

No counterpulsation



Dicrotic Notch = Closure of Aortic Valve and beginning of diastole.

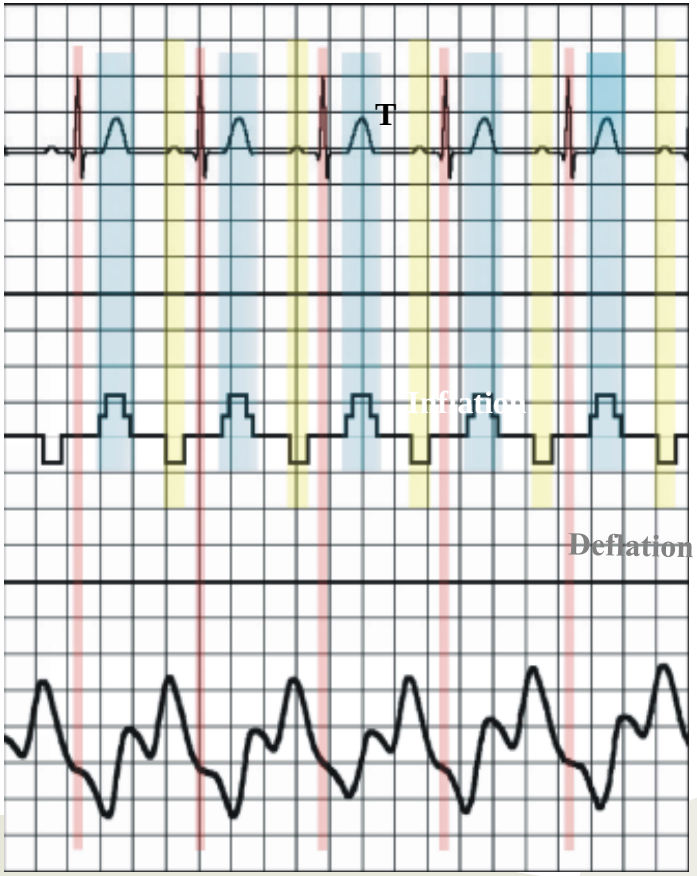
Counterpulsation



Therapeutic augmentation is achieved when **peak** diastolic pressure exceeds **peak** systolic pressure

With ECP, the counterpulsation wave enhances or *augments* diastolic pressure above systolic pressure

RejuvaHeart™



ECP Timing

TRIGGERING:

ECG triggering based on the R-wave detection ensures that inflation occurs in diastole (seen at the apex of the T-wave) and deflation occurs just prior to systole (seen at the apex of the P-wave).

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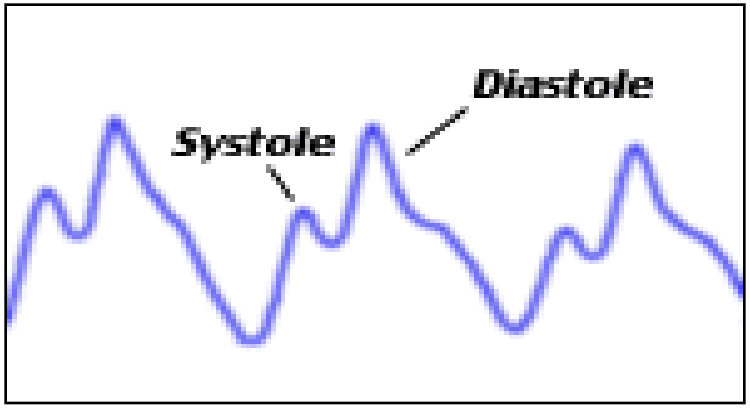
The height of the diastolic peak is compared to the height of the systolic peak. This comparison is represented as *Peak-to-Peak Ratio* or P/P.



The ratio of diastolic augmentation (DA) and systolic unloading (SU) is calculated from the signals measured by the finger plethysmograph.

P/P ratio is calculated as D/S

Long-Term Effects:

While exact mechanism of action is unknown, there are several hypotheses:

- Promotes collateral vessel growth
- Improves endothelial function
- Enhances ventricular function

RejuvaHeart™

	**Endothelin** •Vasoconstrictor
	**BNP** •Promotes diuresis •Released with LV dysfunction
	**Nitric Oxide** •Vasodilator
	**VEGF** •Angiogenesis
	**ANP** •Promotes diuresis

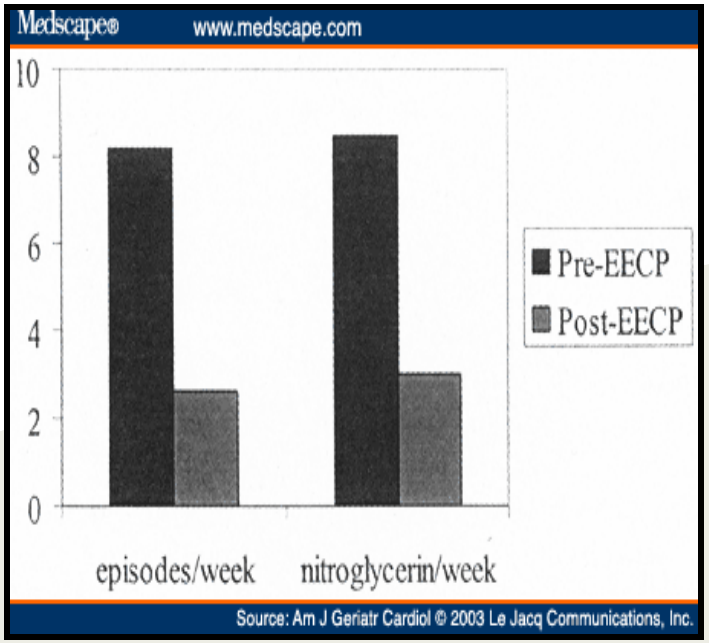
RejuvaHeart™

Subjective Findings:

PATIENTS REPORT:

- Fewer episodes of angina
- Angina pain subsides
- Decreased use or elimination of anti-anginal medications
- Increased exercise tolerance
- Improved ability to perform activities of daily living
- Ability to return to work

Quality of life improvements are the best means for evaluating ECP benefits in the clinical setting.



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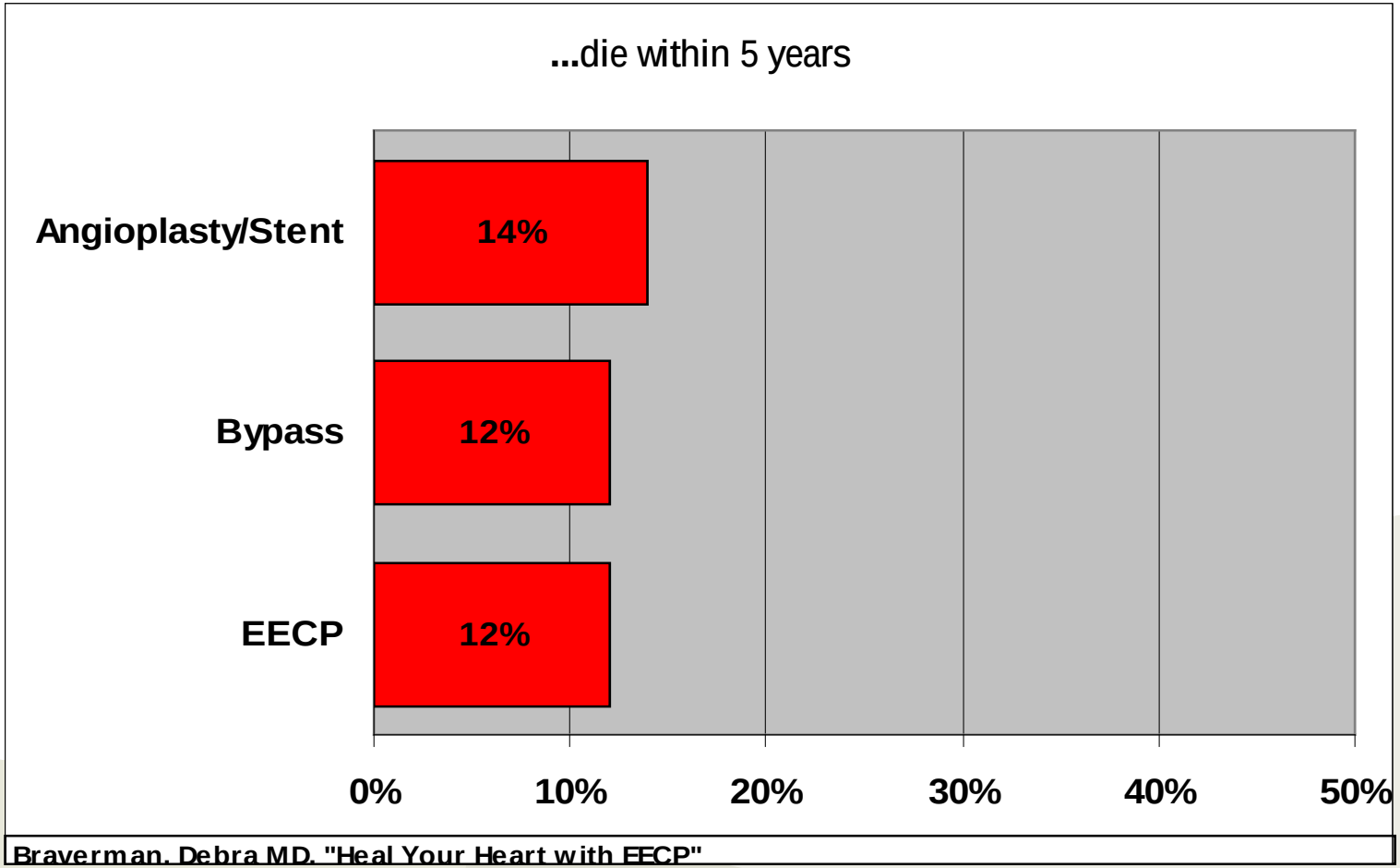
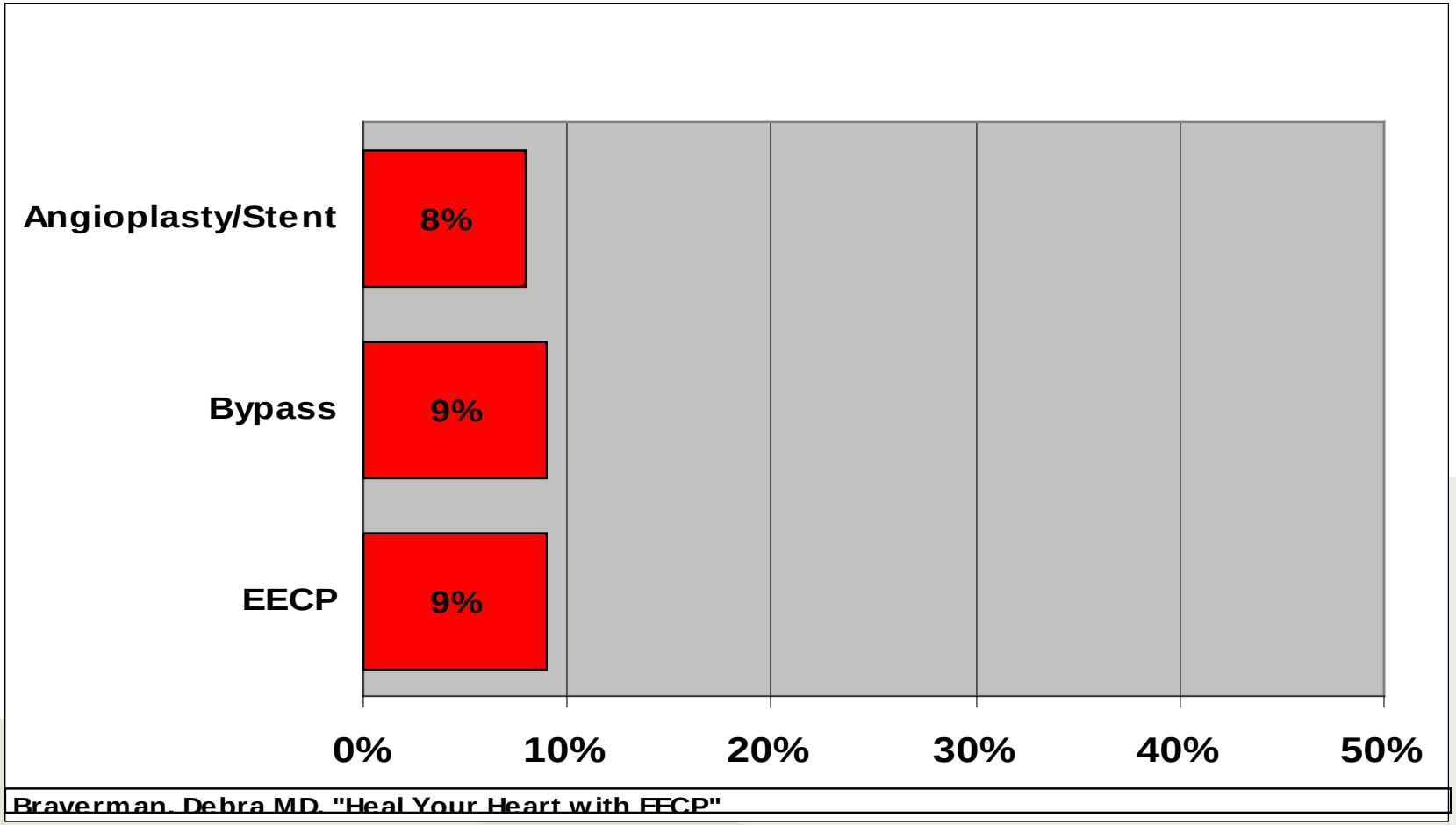
By type of initial procedure, percentage of patients who will …



Braverman, Debra MD. "Heal Your Heart with EECP"

RejuvaHeart™

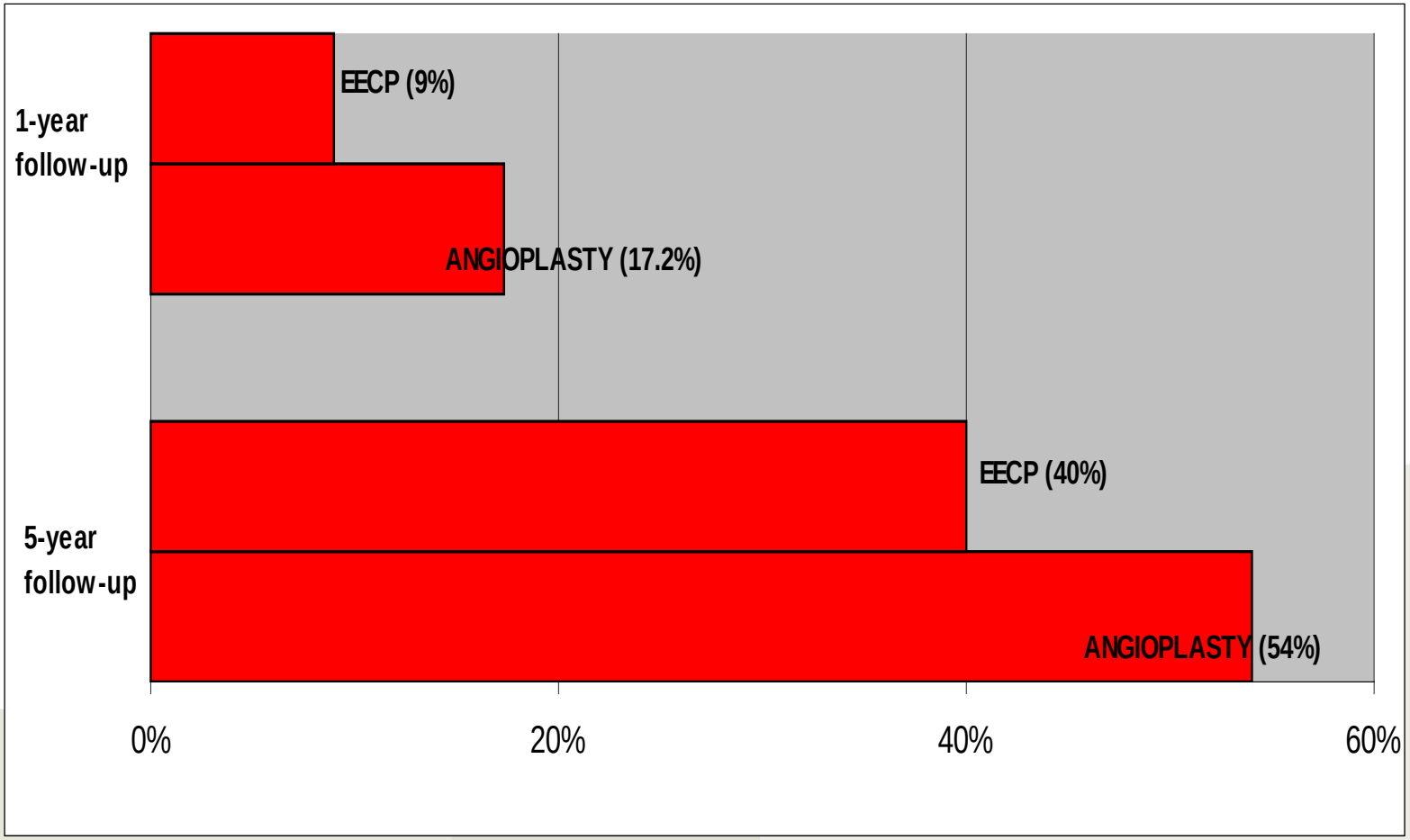
Have a heart attack within the next 5 years:



Braverman, Debra MD. "Heal Your Heart with EECP"

RejuvaHeart™

Repeat treatment rates for ECP vs. Angioplasty patients



RejuvaHeart™

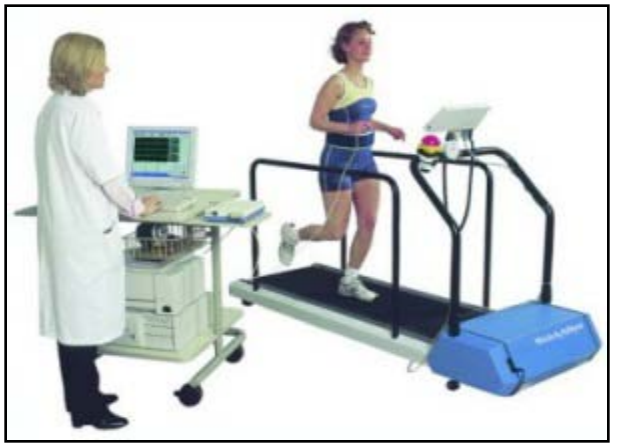
Objective Findings:

THALLIUM SCAN:

Comparisons of scans done before and after **ECP** showed:

- 78% experienced a reduction in ischemia
- 67% showed a complete resolution of perfusion defects

(Efficacy of Enhanced External Counterpulsation in the Treatment of Angina Pectoris, American Journal of Cardiology, 1992)



EXERCISE STRESS TESTS

- 81% of patients showed improved exercise tolerance
- Significant increase in time to ST-segment depression

(Improved Exercise Tolerance following Enhanced External Counterpulsation: Cardiac or Peripheral Effect? General Cardiology 1996)

Enhanced External Counterpulsation Improves Exercise Tolerance in Patients With Chronic Heart Failure

Arthur M. Feldman, Marc A. Silver, Gary S. Francis, Charles W. Abbottsmith, Bruce L. Fleishman, Ozlem Soran, Paul-Andre de Lame, Thomas Varricchione and for the PEECH Investigators

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Enhanced External Counterpulsation Improves Exercise Tolerance in Patients With Chronic Heart Failure

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OBJECTIVES The PEECH (Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure) study assessed the benefits of enhanced external counterpulsation (EECP) in the treatment of patients with mild-to-moderate heart failure (HF).

BACKGROUND Enhanced external counterpulsation reduced angina symptoms and extended time to exercise-induced ischemia in patients with coronary artery disease, angina, and normal left ventricular function. A small pilot study and registry analysis suggested benefits in patients with HF.

METHODS We randomized 187 subjects with mild-to-moderate symptoms of HF to either EECP and protocol-defined pharmacologic therapy (PT) or PT alone. Two co-primary end points were pre-defined: the percentage of subjects with a 60 s or more increase in exercise duration and the percentage of subjects with at least 1.25 ml/min/kg increase in peak volume of oxygen uptake (V_{O_2}) at 6 months.

RESULTS By the primary intent-to-treat analysis, 35% of subjects in the EECP group and 25% of control subjects increased exercise time by at least 60 s ($p = 0.016$) at 6 months. However, there was no between-group difference in peak V_{O_2} changes. New York Heart Association (NYHA) functional class improved in the active treatment group at 1 week ($p < 0.01$), 3 months ($p < 0.02$), and 6 months ($p < 0.01$). The Minnesota Living with Heart Failure score improved significantly 1 week ($p < 0.02$) and 3 months after treatment ($p = 0.01$).

CONCLUSIONS In this randomized, single-blinded study, EECP improved exercise tolerance, quality of life, and NYHA functional classification without an accompanying increase in peak V_{O_2}. (J Am Coll Cardiol 2006;48:1198–205) © 2006 by the American College of Cardiology Foundation

Enhanced external counterpulsation (EECP) is a noninvasive, pneumatic technique that utilizes electrocardiogram-gated diastolic inflation of a series of lower-extremity cuffs to effectively increase diastolic and mean intracoronary pressures as well as coronary flow while reducing systolic pressure in the central aorta and the coronary artery (1). In addition, EECP improves diastolic filling, decreases left ventricular (LV) end-diastolic pressure, and improves LV peak filling rate, end-diastolic volume, and time to peak filling rate (2). This combination of systolic unloading and increased coronary perfusion pressure with external counterpulsation mimics the hemodynamic consequences of intra-aortic balloon counterpulsation. Indeed, EECP was initially evaluated in the treatment of patients with cardiogenic shock (3). Repeated administration of EECP has been shown to have salutary benefits in patients with symptoms of coronary artery disease and normal LV function despite optimal medical therapy (4); patients receiving 35 h of active counterpulsation over a 4- to 7-week period demonstrated reduced angina symptoms and extended time to exercise-induced ischemia, when compared with a group of patients randomized to receive sham counterpulsation (4). In addition, EECP effected a significant improvement in health-related quality of life up to 12 months after completion of treatment (5). Although the specific mechanisms responsible for the beneficial clinical effects of EECP therapy in patients with symptomatic coronary artery disease remain unclear, recent studies have demonstrated that a positive

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Abbreviations and Acronyms

EECP = enhanced external counterpulsation
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
MLWHF = Minnesota Living with Heart Failure
NYHA = New York Heart Association
PEECH = Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure trial
PT = protocol-defined pharmacologic therapy
V_{O_2} = oxygen uptake

response to EECP is associated with enhanced peripheral endothelial function (6). In addition, EECP improved stress myocardial perfusion both at baseline and at maximal exercise levels (7), reduced plasma levels of brain natriuretic peptides (2), and improved regional myocardial oxygen metabolism (8).

In the initial clinical evaluations of EECP, patients were required to have normal LV function. However, several studies suggested that EECP might also benefit patients with LV dysfunction. Approximately 22.3% of patients enrolled in a voluntary registry of patients undergoing EECP therapy for treatment of angina pectoris had LV dysfunction as evidenced by a left ventricular ejection fraction (LVEF) of ≤35% (9). These patients had increased severity of angina symptoms and higher rates of the composite outcome of death/myocardial infarction/or revascularization as compared with patients with preserved ventricular function. However, patients who did not have an outcome event had improved anginal status and nitroglycerin use that was comparable to that seen in patients with normal LV function. Furthermore, EECP improved exercise capacity and quality of life without adverse consequences in a small group of patients with stable heart failure (HF) who underwent 35 sessions of EECP (10). To address the efficacy of EECP in patients with symptomatic HF secondary to systolic dysfunction, we conducted a multicenter, controlled clinical trial comparing protocol-defined pharmacologic therapy (PT) (per published guidelines) with 35 1-h sessions of EECP with PT alone.

METHODS

The PEECH (Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure) trial was conducted at 29 centers in the U.S. and the U.K. The complete protocol has been described elsewhere (11). Enrollment criteria included New York Heart Association (NYHA) functional class II to III symptoms secondary to either ischemic or nonischemic cardiomyopathy, LVEF ≤35%, and PT consisting of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker (for at least 1 month) and a beta-blocker (for at least 3 months) unless they were not tolerated. Digoxin, diuretics, and other medications used to treat HF could be given at the investigator's discretion. After providing written informed consent, eligible patients were randomized in a 1:1 ratio to treatment with EECP or to continued PT. The study personnel responsible for evaluating study subjects as well as the steering committee, the end points committee, the exercise core laboratory, and the sponsor were unaware of the treatment assignments. Other personnel at the study centers were not blinded to the randomization and were charged with providing clinical care and assessing adverse experiences. Study files were organized to preserve blinding of the investigators responsible for evaluating the subjects.

Patients randomly assigned to EECP received 35 1-h sessions over a period of 7 to 8 weeks. Three pneumatic cuffs were placed around the lower limbs and buttocks and were inflated sequentially upward at the onset of diastole, and released rapidly and simultaneously before the onset of systole. The protocol-specified applied pressure was 300 mm Hg and was reached within 5 min of the initiation of treatment. Pulse oximetry was monitored continuously during the treatment session, and the subject's clinical status was re-evaluated if the oxygen saturation dropped by ≥4%. Patients in both treatment groups were seen in follow-up at 1 week, 3 months, and 6 months after treatment.

The 2 co-primary end points were the percentage of subjects with at least a 60-s increase in exercise duration from baseline and the percentage of subjects with at least a 1.25-ml/min/kg increase in peak volume of oxygen uptake (V_{O_2}) from baseline to 6 months. The exercise test was standardized across all centers using a modified Naughton protocol and a calibrated treadmill. Peak V_{O_2} was defined as the oxygen consumption observed at the maximum level of exercise, as shown by a respiratory exchange ratio (RER) >1, a rating of >14 using the Borg scale of perceived exertion (15-point, 6 to 20 scale), and identifying the anaerobic threshold, when reached. Raw exercise data were analyzed by a core exercise laboratory, blinded to treatment assignment and sequence, which provided the results used in the analysis. Secondary end points included change in exercise duration, peak V_{O_2}, NYHA functional class status, quality of life, and the occurrence of cardiovascular clinical outcomes during the treatment phase and the 6-month follow-up. The NYHA functional classification was assessed and graded by the blinded investigator at each participating site. Quality of life was assessed using the Minnesota Living with Heart Failure (MLWHF) instrument (12).

Primary analysis was by intent-to-treat, and data from patients who did not complete the study were analyzed by carrying forward the last observation. In a secondary analysis, data from patients who withdrew before reaching the 6-month end point were censored at the time of the last evaluation. The primary analysis was a logistic regression which factors site and baseline. Other variables were analyzed using the Cochran-Mantel-Haenszel test, adjusted for investigator. Continuous variables were analyzed using an

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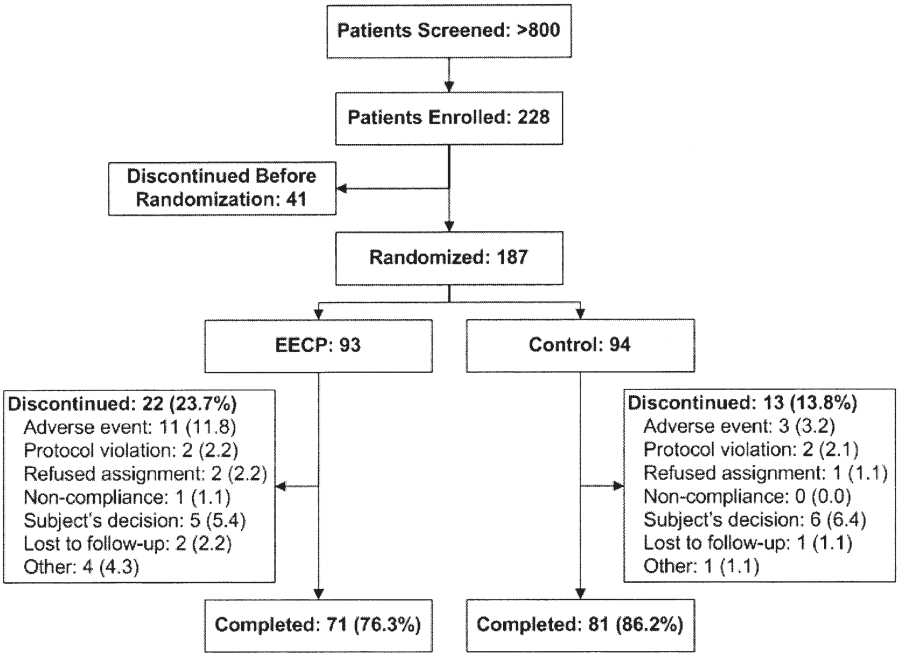

Figure 1. Enrollment and follow-up of patients in the PEECH study. EECP = enhanced external counterpulsation.

analysis of variance, with treatment as a main effect and investigator as a blocking factor. Treatment by investigator interaction was tested at the 0.1 level of significance. The treatment comparison of the 2 co-primary parameters (exercise duration and peak Vo_2) was made according to Hochberg's closed testing procedure (13), with control of the overall type 1 error at 0.05.

Assumptions with respect to the sample size have been described previously (11). The trial was designed to detect at least a 60-s increase from baseline in 50% of EECP patients compared with 20% of control patients and a 1.25 ml/min/kg increase in peak Vo_2 in 50% of EECP patients compared with 30% of control patients. Under these design assumptions, the study had a 90% power to detect a statistically significant difference at the 0.025 level of significance and was designed to be positive if there was a statistically significant difference in either primary end point at the 0.025 level or in both end points at the 0.05 level.

The study was managed by an independent coordinating center (Anabase International Corporation, Stockton, New Jersey) who performed the statistical data analysis. The sponsor had no role in the data collection or analysis. A steering committee oversaw the scientific and clinical aspects of the study. Exercise data were conveyed to an independent core laboratory where study quality and data results were analyzed. Medical staff at the coordinating center were trained to assess the quality of data and tracings from the cardiopulmonary exercise tests and, together with the core laboratory, monitored performance of the testing and instructed sites to repeat when necessary to obtain a fully evaluable test. A data and safety monitoring board oversaw all safety aspects of the study, and an independent clinical end-points committee classified adverse events. The study was approved by the institutional review board of each participating center and was conducted according to the Declaration of Helsinki.

RESULTS

Between March 2001 and February 2004, 187 patients were randomized (93 to EECP and 94 to PT alone) (Fig. 1). There were no significant differences in baseline variables or background therapy between the 2 treatment groups

Table 1. Baseline Patient Characteristics*

Characteristics	EECP	PT Control
Number of patients	93	94
Men, n (%)	72 (77.4)	71 (75.5)
Race, Caucasian, n (%)	76 (81.7)	75 (79.8)
Age (mean yrs, SD)	62.4 (11.7)	63.0 (10.4)
Etiology, ischemic, n (%)	64 (68.8)	66 (70.2)
NYHA, n (%)		
Functional class II	60 (64.5)	62 (66.0)
Functional class III	33 (35.5)	32 (34.0)
Heart rate, beats/min (SD)	70.7 (11.2)	70.6 (12.0)
Blood pressure, mm Hg (SD)		
Systolic	116.7 (17.7)	114.8 (18.4)
Diastolic	70.9 (10.2)	70.8 (10.8)
LVEF, mean % (SD)	25.9 (6.1)	26.7 (6.5)
Number of patients completing protocol	80	84
Exercise duration, s (SE)	610.6 (27.8)	570.9 (26.1)
Peak Vo_2, ml/kg/min (SE)	14.7 (0.4)	14.1 (0.4)
RER (mean, SE)	1.04 (0.01)	1.04 (0.01)
VE, l/min	47.9 (1.8)	46.9 (1.6)
Borg scale score, mean (SE)	16.7 (0.2)	16.6 (0.2)

*There was no significant difference between groups.

EECP = enhanced external counterpulsation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PT = protocol-defined pharmacologic therapy; RER = respiratory exchange ratio; VE = minute ventilation; Vo_2 = volume of oxygen uptake; + = sitting blood pressure.

Table 2. Protocol-Defined Pharmacologic Therapy Utilization Rate and Dose Equivalents at Baseline*

HF Treatment	EECP	PT Control
ACE inhibitors, n (%)	70 (75.3)	73 (77.7)
Enalapril daily dose equivalent (mg)		
Mean (SD)	11.8 (10.1)	13.5 (9.9)
Median	10	10
ARBs, n (%)	18 (19.4)	18 (19.1)
Losartan daily dose equivalent (mg)		
Mean (SD)	63.2 (42.0)	60.5 (38.5)
Median	50	50
Beta-blockers, n (%)	79 (84.9)	81 (86.2)
Carvedilol daily dose equivalent (mg)		
Mean (SD)	39.4 (29.7)	39.7 (30.1)
Median	25	25

*There were no significant differences between groups.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure. Other abbreviations as in Table 1.

(Tables 1 and 2). Patients were predominantly Caucasian men with NYHA functional class II HF symptoms who had a mean ejection fraction of 26 ± 6%. Utilization rates of background pharmacologic therapy and average equivalent doses at baseline demonstrated compliance with guideline-recommended therapy (Table 2). Although medication changes occurred in individual patients during the trial, there were no significant differences between treatment groups, and average equivalent doses remained the same at each time point. In particular, there were no differences in diuretic dosing during the study (data not shown).

Exercise duration increased by 60 s or more in 35.4% of patients in the group assigned to EECP as compared with 25.3% of patients in the pharmacologic treatment group at the 6-month follow-up visit ($p = 0.016$) (Fig. 2). By contrast, the percentage of subjects who demonstrated an increase in peak V_{O_2} of ≥1.25 ml/kg/min did not differ between the 2 treatment groups (22.8% vs. 24.1%) at the same visit. EECP treatment was also associated with a significant increase in exercise time at 1 week, 3 months, and 6 months when compared with those patients receiving pharmacologic therapy alone (Table 3). While there was a trend at 1 week and 3 months, EECP did not effect a significant increase from baseline in peak V_{O_2} at any time point. Similarly, there was no change in ventilatory equivalent for carbon dioxide (Ve/VCO_2) at any time point (data not presented). There were no between-group differences in RER or Borg score (overall median = 17) at baseline or any follow-up time points. However, there were differences in ventilatory response at 1 week and 3 months after treatment (Table 3). The benefit of EECP on exercise duration was also evident when data from patients who withdrew from the study were censored at the time of the last visit (data on file). Analysis of site interaction on the primary end points yielded no statistically significant differences. In addition, evaluation of the primary end point at those sites with larger enrollments demonstrated results that were consistent with the overall study results. Consistent with an improvement in exercise time, EECP also effected a significant improvement in NYHA functional class and quality of life. The percentage of patients who demonstrated an improvement in NYHA symptoms was significantly larger in the group receiving EECP than in patients receiving pharmacologic therapy alone at 1 week, 3 months, and 6 months after therapy (Fig. 3). Similarly, EECP effected a statistically significant improvement in quality of life as measured by the MLWHF questionnaire at 1 week and 3 months after completion of EECP therapy, but not at

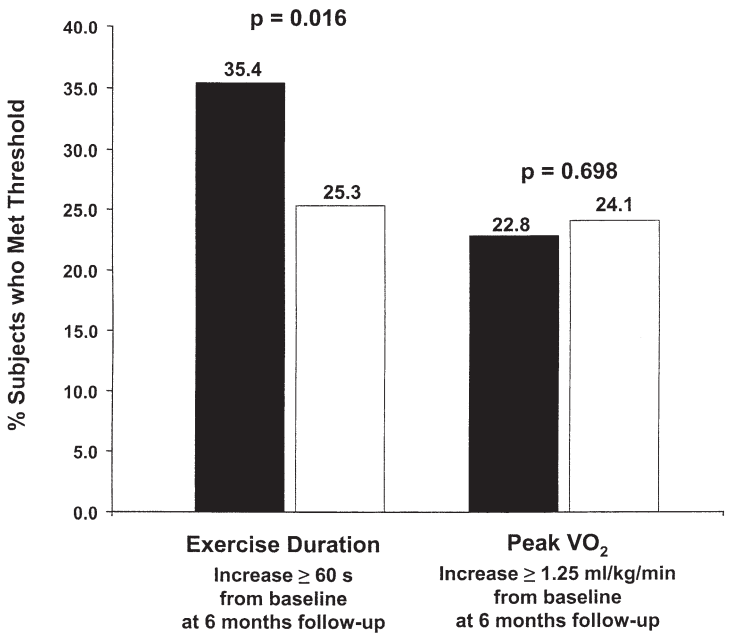

Figure 2. The percentage of patients who had at least a 60-s increase from baseline in exercise duration and the percentage of patients with at least a 1.25 ml/kg/min from baseline at 6 months after treatment (co-primary end points; intent-to-treat analysis, last observation carried forward). V_{O_2} = oxygen uptake. **Solid bar** = enhanced external counterpulsation; **open bar** = control subjects.

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Table 3. Mean Change From Baseline in Exercise Duration and Peak Vo_2

	EECP		PT Control		
	No.	Mean Change ± SE	No.	Mean Change ± SE	p Value*
1-Week Follow-Up					
Change exercise duration (s)	77	26.4 ± 12.2	78	−5.5 ± 11.7	0.010
Ischemic	53	24.6 ± 15.7	54	−16.7 ± 14.2	0.007
Nonischemic	24	30.2 ± 18.3	24	19.9 ± 20.3	0.836
Change in peak Vo_2 (ml/kg/min)	77	0.1 ± 0.3	78	−0.4 ± 0.3	0.071
Ischemic	53	0.2 ± 0.4	54	−0.7 ± 0.4	0.008
Nonischemic	24	−0.2 ± 0.5	24	−0.4 ± 0.5	0.987
Change in RER	77	0.01 ± 0.01	78	0.00 ± 0.01	0.363
Change in VE (l/min)	77	0.4 ± 1.0	78	−2.1 ± 1.0	0.011
3-Month Follow-Up					
Change exercise duration (s)	78	34.5 ± 13.9	82	−7.0 ± 12.7	0.014
Ischemic	54	34.2 ± 17.2	57	−17.3 ± 13.1	0.017
Nonischemic	24	35.4 ± 23.8	25	16.7 ± 28.9	0.741
Change in peak Vo_2 (ml/kg/min)	78	0.2 ± 0.3	82	−0.4 ± 0.3	0.119
Ischemic	54	−0.0 ± 0.4	57	−0.4 ± 0.3	0.122
Nonischemic	24	0.6 ± 0.5	25	−0.2 ± 0.8	0.437
Change in RER	78	0.00 ± 0.01	82	−0.01 ± 0.01	0.252
Change in VE (l/min)	78	0.5 ± 0.9	82	−2.3 ± 1.2	0.010
6-Month Follow-Up					
Change exercise duration (s)	79	24.7 ± 15.2	83	−9.9 ± 13.2	0.013
Ischemic	54	20.6 ± 18.5	57	−25.8 ± 13.9	0.010
Nonischemic	25	33.5 ± 26.8	26	24.7 ± 28.3	0.724
Change in peak Vo_2 (ml/kg/min)	79	−0.3 ± 0.3	83	−0.6 ± 0.3	0.315
Ischemic	54	−0.4 ± 0.3	57	−0.9 ± 0.3	0.115
Nonischemic	25	−0.3 ± 0.5	26	0.2 ± 0.6	0.935
Change in RER	79	0.00 ± 0.01	83	0.00 ± 0.01	0.161
Change in VE (l/min)	79	−0.8 ± 1.0	83	−2.4 ± 1.1	0.094

Intent-to-treat analysis, last observation carried forward. *p value was obtained from analysis of covariance with main effects etiology, investigator, and etiology by investigator, if significant, and covariate baseline value.

Abbreviations as in Table 1.

6 months after treatment (Fig. 3). Analysis of changes in improvement in NYHA functional classification and quality of life did not change when data from patients who withdrew from the study were censored at the time of withdrawal (data on file).

We assessed whether differences existed in response to EECP therapy in patients with HF secondary to either ischemic or nonischemic dilated cardiomyopathy. Albeit, in a relatively small sample size, subgroup analysis based on etiology of disease demonstrated benefit in patients with ischemic cardiomyopathy, while this difference was not seen in the small number of patients with nonischemic disease (Table 3). Similarly, when assessing the effects of EECP on NYHA functional classification, there was a greater proportion of patients showing improvement in the EECP group when compared with those receiving pharmacologic therapy alone at all time points in the group with ischemic disease (1 week: 37.0% EECP vs. 12.7%, $p = 0.004$: 3 months: 34.5% vs. 12.3%, $p = 0.025$; 6 months: 36.4% vs. 15.5%, $p = 0.026$). In addition, quality of life was significantly improved in the ischemic group at 3 months of follow-up (−6.5 ± 3.2 EECP vs. −1.5 ± 2.1 PT, $p = 0.046$) but not at any time point in patients receiving EECP who had a nonischemic etiology. However, no significant differences in the parameters of exercise duration, peak Vo_2, functional classification, or quality of life were detected within treatment assignment subgroups.

We also performed a post-hoc analysis to assess whether any predictors of response to EECP were identifiable. Analysis of co-primary end point responder rates based upon age, gender, race, etiology, NYHA functional classification, LVEF, height, weight, and body mass index above versus below median values were performed. No statistically significant differences were found between responders and nonresponders in the EECP group, while younger age ($p = 0.004$), female gender ($p = 0.006$), higher LVEF ($p = 0.027$), and less weight ($p = 0.027$) predicted response in the control group.

Fewer patients completed the study in the active treatment group (76%) than in the control group (86%), largely due to more patients in the EECP group discontinuing due to an adverse experience (11.8% EECP vs. 3.2% PT). Adverse events that occurred in relation to the application of EECP therapy resulting in discontinuation included sciatica (1 patient), leg pain (1 patient), and arrhythmia, which interfered with application of the therapy (2 patients). One other EECP subject suffered a non–Q-wave myocardial infarction during the treatment period not attributable to

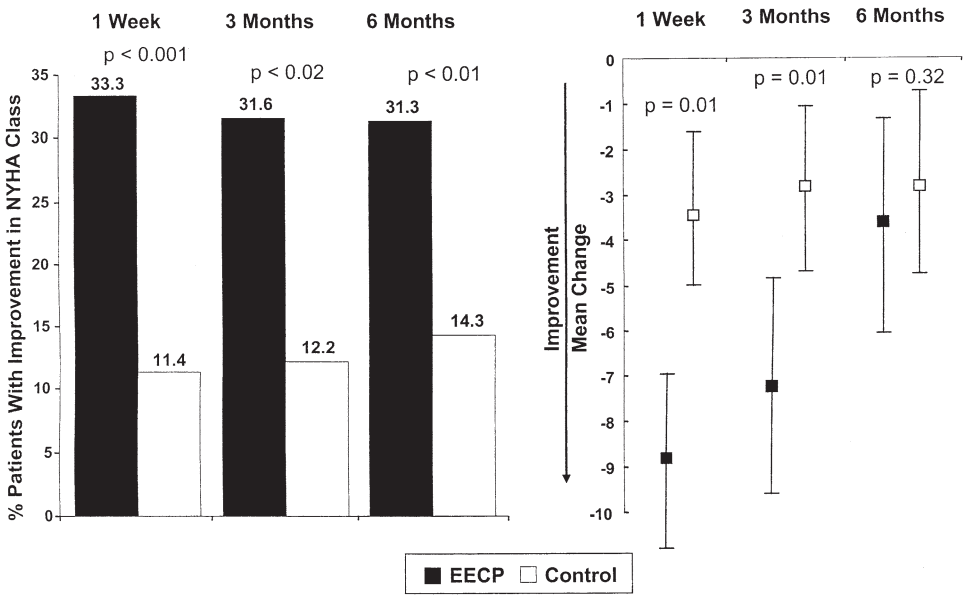

Figure 3. Percentage of patients who improved in their New York Heart Association (NYHA) functional class **(left)** and mean change in quality-of-life score **(right)** at 1 week, 3 months, and 6 months compared with baseline. EECP = enhanced external counterpulsation.

the therapy. During the follow-up period, 6 additional subjects from the EECP group discontinued due to worsening HF (4 patients), biventricular pacemaker implantation (1 patient), and worsening lung cancer (1 patient). Adverse events in the control group leading to discontinuation included 2 deaths during the treatment period and 1 instance of atrioventricular block during the follow-up period.

However, the number of pre-defined clinical events that occurred during the trial was not different between the group of patients who received EECP and those in the control group (Table 4). In addition, the number of adverse events and the number of serious adverse events were equal in the 2 treatment groups. The number of subjects randomized to EECP therapy that experienced any adverse event or a serious adverse event was nearly identical to that in the pharmacologic therapy group. Two patients had serious adverse events that the site investigator attributed to EECP during the treatment period: 1 patient experienced worsening HF while a second patient developed a pulmonary embolism. During the post-treatment period, an additional patient developed a deep venous thrombosis that was attributed by the investigator to EECP. A temporary decrease in oxygen saturation observed by pulse oximetry occurred in 11 (12.4%) subjects in 30 (1%) of 2,859 EECP therapy sessions administered during the trial. Except for 1 case of oxygen desaturation followed by a worsening of HF after the treatment session, all other episodes were reversed by a protocol-mandated brief interruption of the treatment session and improved breathing.

DISCUSSION

The results of the PEECH trial demonstrate that 35 1-h sessions of EECP over a period of 7 weeks benefited patients with mild-to-moderate HF and systolic LV dysfunction who were receiving PT. Enhanced external counterpulsation effected a statistically significant increase ($p = 0.016$) in the percentage of patients exceeding a 60-s improvement in exercise time, making this a positive trial based on the predefined statistical criteria for the primary end-point analysis. However, it must be noted that EECP did not alter the percentage of patients demonstrating an increase of ≥1.25 ml/kg/min in peak Vo_2. Consistent with the improvement in the percentage of patients exceeding a 60-s improvement in exercise time, patients receiving active therapy also demonstrated a modest increase in exercise time when assessed as increase from baseline and an improvement in NYHA HF symptoms. These benefits of EECP were demonstrable after completion of EECP therapy as well as for up to 6 months. The active treatment group also reported an improvement in quality of life that was sustained for 3 but not 6 months. Peak Vo_2, when measured as change from baseline, showed a trend towards benefit in the active treatment group at 1 week and 3 months, but there was not a statistically significant difference between the 2 study groups.

Overall, the use of EECP was well tolerated. Two patients had serious adverse events during the treatment period. One patient had a pulmonary embolism. Because EECP "milks" the vasculature of the lower extremities, this is a recognized side effect and points out that patients at risk for deep venous thrombosis should be carefully evaluated before undergoing EECP therapy and monitored closely during the course of treatment. A second patient experienced worsening HF. This may have been secondary to increased venous load during EECP therapy. A larger number of patients withdrew from the study in the EECP group due to adverse events, most of which were associated

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Table 4. SAEs*

	EECP	PT Control
Subjects with SAEs, n (%)	27 (30.3)	26 (29.5)
Occurring during treatment period		
Subjects with SAEs, n (%)	7 (7.9)	8 (9.1)
SAEs related to treatment		
WHF	1	
Pulmonary embolism	1	
Occurring during follow-up		
Subjects with SAEs, n (%)	21 (23.6)	23 (26.1)
SAEs related to treatment		
WHF		1
Deep venous thrombosis	1	
Pre-defined clinical events	89	88
WHF with IV, n (%)	8 (9.0)	12 (13.6)
WHF with no IV, n (%)	8 (1.1)	4 (2.3)
ACS, n (%)	1 (1.1)	0 (0.0)
MI, n (%)	4 (4.5)	0 (0.0)
Cardiovascular death, n (%)	0 (0.0)	2 (2.3)

*There were no significant differences between groups.

ACS = acute coronary syndrome, non-MI; EECP = enhanced external counterpulsation; MI = myocardial infarction; PT = protocol-defined pharmacologic therapy; SAEs = serious adverse events; WHF = worsening heart failure; WHF with IV = worsening heart failure, hospitalized, requiring IV therapy; WHF with no IV = worsening heart failure not requiring IV therapy.

with the application of EECP. Some patients experienced discomfort that obviated their continued participation. However, it is noteworthy that the number of adverse events or serious adverse events did not differ between the 2 study groups over the course of the trial.

The design of the PEECH trial was influenced by concerns that "sham" EECP altered vascular hemodynamics. Indeed, even low-pressure EECP is associated with a marked increase in right ventricular filling, while not associated with a decrease in peripheral vascular resistance (A.D. Michael, unpublished data, November 2003). Thus, investigators were concerned that "sham" EECP might actually increase the incidence of HF because increased right ventricular loading would not be offset by decreased peripheral vascular resistance. Furthermore, it was observed in the MUST EECP (Multicenter Study of Enhanced External Counterpulsation) trial that changes in exercise time were seen in patients treated with "sham" EECP (4). Thus, we believed that EECP could only be evaluated using an unblinded control group. To obviate bias on the part of investigators, each study site had 2 separate teams, an investigative team and a patient care team, and both patients and coordinators were educated regarding the need for confidentiality between the members of these 2 groups. Furthermore, study coordinators who came into contact with the patient on a daily basis during active treatment were instructed not to address clinical issues with their patients. Thus, assiduous efforts were undertaken to separate the study team from the clinical care team, consistent with the single-blind trial design. That there was consistency across all study centers with respect to protocol mandates was evidenced by the fact that there were no intercenter differences in study results. However, this design may not mitigate against the possibility that daily visits for a period of 7 weeks might have benefited patients in the active treatment group.

The finding that EECP increased exercise time but did not effect a statistically significant change in peak Vo_2 raises an interesting conundrum. One possible explanation for this disparity is that the beneficial effects of EECP in the PEECH study were attributable to a "placebo" effect in the active treatment group in view of the fact that these patients were not blinded to their treatment assignment. The finding that significant improvements in quality-of-life scores decreased over time in the EECP group is also suggestive of a placebo effect. Alternatively, we may have underpowered the trial for a change in peak Vo_2 as there was a trend towards an increase in peak Vo_2 at both 1 week and 3 months, though these trends did not reach statistical significance. Metra et al. (14) recently found that treatment with carvedilol effected a significant improvement in exercise duration without an accompanying change in peak Vo_2 in a small group of optimally medicated patients with predominantly NYHA functional class II to III HF symptoms. It is unlikely that our failure to see a change in peak Vo_2 was due to our selection of thresholds as the thresholds of $\geq$60 s improvement in exercise duration and $\geq$1.25 ml/kg/min improvement in peak Vo_2 were significantly greater than what had been observed in control groups of major HF treatment trials reported before the planning phase of this trial.

In summary, EECP improved exercise tolerance and HF symptoms in patients with NYHA functional class II and III HF who were receiving PT but did not improve peak Vo_2. Because patients were not blinded to therapy, these benefits of EECP may be attributable to a "placebo" effect. However, the usefulness of EECP by physicians must be individualized based on their assessment of the totality of EECP data. Further studies may help elucidate both the mechanism of action and the overall effects of EECP therapy.

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APPENDIX

For a list of the investigators participating in the PEECH study, please see the online version of this article.

Enhanced External Counterpulsation Improves Exercise Tolerance in Patients With Chronic Heart Failure

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Enhanced External Counterpulsation as Initial Revascularization Treatment for Angina Refractory to Medical Therapy

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Key Words
External counterpulsation · Registry · Angina · Noninvasive circulation assist device · Revascularization

Abstract
Enhanced external counterpulsation (EECP) is effective in patients with angina refractory to medical therapy or revascularization. However, as a noninvasive treatment it should perhaps be considered the first-line treatment with invasive revascularization reserved for EECP failures or high-risk patients. The International EECP Patient Registry was used to analyze a cohort of patients with prior percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) (n = 4,454) compared with a group of patients (PUMPERS) who were candidates for PCI and/or CABG and chose EECP as their initial revascularization treatment (n = 215). The PUMPERS responded to treatment with EECP with decreased anginal episodes and nitroglycerin use and with improvement in their Canadian Cardiovascular Society functional class, similarly to previously revascularized patients. Treatment with EECP resulted in sustained, and often progressive, reduction in angina over the succeeding 6 months. Given the findings of this study, it is interesting to speculate on the possibility of using EECP as the primary revascularization intervention after medical therapy proves unsatisfactory.

Background

Enhanced external counterpulsation (EECP) has become increasingly used as a noninvasive treatment option for angina pectoris patients refractory to medical therapy who are not candidates for revascularization. Patients treated with EECP therapy have demonstrated an improvement in Canadian Cardiovascular Society (CCS) functional angina class, increased exercise tolerance, and a reduction in nitroglycerin use. Objective measures of coronary ischemia have demonstrated improved time to ST segment depression, stress myocardial perfusion [1–4], PET scan myocardial perfusion at rest and after dipyridamole [5]. These benefits have been demonstrated to be durable in many patients for up to 5 years after treatment [6, 7].

EECP studies have demonstrated a greater improvement in stress myocardial perfusion in patients with single- or double-vessel disease or multiple conduits with prior coronary artery bypass graft (CABG) compared to patients with unrevascularized severe triple-vessel disease [8, 9]. Also, patients undergoing EECP after prior CABG demonstrate improvement equal to post-percutaneous coronary intervention (PCI) patients. This is noted despite the post-CABG patients having more extensive disease and greater left ventricular dysfunction at the time of EECP treatment [10]. These findings support an 'open-vessel hypothesis', i.e. that a patent vessel is necessary to transmit the increased diastolic pressure and flow gener-

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ated by EECP to the distal coronary circulation and promote the recruitment or development of collaterals.

Current health care policies usually limit reimbursement for EECP to patients with angina refractory to medical therapy who are not candidates for CABG or PCI. Because of this, the patients currently selected for EECP treatment tend to be those with extensive severe disease, a group in which it has been historically hardest to show benefit.

There are no data evaluating the strategy of EECP used as the primary revascularization (no prior CABG or PCI) for patients with medically refractory angina. As an effective and noninvasive treatment, EECP should perhaps be considered prior to invasive revascularization procedures, particularly in limited coronary disease with preserved left ventricular function where the main benefit of revascularization is angina relief and improved quality of life.

Patients selecting EECP as primary revascularization, often with limited coronary disease, may demonstrate a greater benefit than the more commonly treated refractory angina patient with extensive coronary artery disease. The effect of EECP in decreasing oxidative stress, normalizing endothelial dysfunction, and promoting favorable remodeling may be particularly beneficial in the earlier stages of atherosclerotic disease [11]. Less extensive disease might favor collateral formation or recruitment as per the patent-vessel hypothesis. It is also possible, however, that the absence of the additional conduits provided by prior CABG might limit the potential for distal transmission of the increased pressure and flow generated by EECP, thus limiting recruitment and development of collaterals. Primary treatment with EECP might also, in a fashion analogous to angioplasty compared to CABG, lead to an increased infarct mortality when compared to CABG due to fewer distal conduits and less well developed collaterals resulting in larger infarcts.

The International EECP Patient Registry (IEPR) was initiated in 1998 to determine the baseline characteristics, safety and acute and long-term outcome of EECP therapy in consecutive series of patients undergoing treatment for chronic angina in a wide variety of clinical settings [12]. Patients are being followed for 3 years after a course of treatment. As of July 2001 there were 89 clinical sites, both in the United States and abroad that had enrolled over 5,000 patients into the registry. While most patients treated in the International EECP registry have angina refractory to medical therapy and are not revascularization candidates, the IEPR also includes patients who were candidates for CABG and/or PCI and chose EECP as their primary revascularization therapy. This subgroup of patients were given the acronym 'PUMPER' representing Primary Utilization to improve Myocardial Perfusion with Enhanced external counterpulsation Revascularization, and the effectiveness of this approach was analyzed in the following report.

Methods

The IEPR was used to analyze a cohort of patients enrolled into the registry prior to September 2000 who had data with respect to previous CABG and PCI, as well as judgment as to suitability for such interventions as determined by their referring physicians at the time when patients began their EECP treatment. The group with prior PCI and/or CABG revascularization (non-PUMPER) was compared (patient characteristics, treatment course, results, morbidity and mortality) with the group of patients choosing EECP as their initial revascularization treatment (PUMPER). All patients had reached their 6 months' post-treatment follow-up time-point to be included in the analysis.

Statistical Methods

Data on proportions were calculated as percentages of the number of patients having a response for that attribute. Continuous variables were expressed as mean value and standard deviation for those patients reporting that variable. Comparisons of proportions in the two groups having an attribute were done using χ^2 or Fisher's exact tests. Comparison of continuous variables was performed using the Wilcoxon t test approximation. All statistical analysis was carried out using the SAS® system.

Results

Of the 4,454 patients in the registry suitable for analysis, 4,239 (95%) had undergone revascularization at some time prior to EECP (non-PUMPER). Of those who had previously undergone revascularization, 79.3% had prior CABG, 75% had prior PCI, 54% had both. Only 16% of these patients were considered suitable for further invasive revascularization at the time of beginning EECP. In contrast, 215 patients (5%) had no previous revascularization (PUMPER), and were usually also considered suitable either for CABG (90%) or PCI (70%) at the time of beginning EECP. Demographics, medical history and risk factors are shown in table 1. Both groups were composed of predominantly white males with a mean age of 66.5 years for the non-PUMPER and 67.4 years for the PUMPER. PUMPER were significantly more likely to be nonwhite, had significantly fewer risk factors than the non-PUMPER group, and had fewer concomitant conditions such as congestive heart failure and diabetes. As shown in table 1, the PUMPER group had coronary artery disease of more recent onset (5.1 vs. 11.6 years, $p < 0.001$)

Table 1. Demographics, medical history, risk factors, coronary disease, angina and nitroglycerin use before EECP treatment

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Demographics		
Age (mean), years	66.4 ± 10.7	67.1 ± 11.0
Male, %	75.4	72.9
White race, %**	94.0	86.4
Risk factors, %		
Family history	77.0	73.2
Diabetes***	43.3	32.0
Hypertension	69.6	65.9
Hyperlipidemia**	79.0	68.6
Smoking (past or current)*	71.7	62.7
Medical history		
Prior myocardial infarction, %***	71.3	40.0
Non-cardiac vascular disease, %***	31.5	19.8
Congestive heart failure, %***	32.9	13.0
LVEF, mean %***	46.2	52.5
Duration of CAD, years***	11.6 ± 8.1	5.1 ± 6.6
Multivessel disease (≥ 70% stenosis), %***	78.2	52.0
Prior treatment, %		
Prior CABG or PCI	100.0	0
Prior EECP	4.4	0
Suitability for revascularization		
Candidate for CABG***	12.7	89.8
Candidate for PCI***	12.8	70.1
Candidate for neither***	83.6	0
CCS angina class, %***		
Class I	2.6	9.3
Class II	13.5	33.0
Class III	59.3	44.2
Class IV	24.6	13.0
Unstable angina, %	3.4	2.3
Angina episodes/week***	10.4 ± 13.1	6.4 ± 9.7
Nitroglycerin use, %***	71.4	46.9
Number of times/week*	9.8 ± 12.4	7.1 ± 10.5

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

and less multivessel disease (52.0 vs. 78.2%, $p < 0.001$). PUMPER had less severe angina (class III/IV angina in 57.2 vs. 83.9%, $p < 0.001$) and less nitroglycerin use (46.9 vs. 71.4%, $p < 0.001$). Angina characteristics and nitroglycerin use are summarized in table 1.

Patients underwent a mean treatment time of 34 h. There was no significant difference in the course of treatment completion rates of PUMPER versus non-PUMPER (88.8 vs. 82.8%). The magnitude of the hemodynamic effect produced by EECP was significantly higher in the PUMPER group as assessed by the effectiveness ratio [13], which is defined as the ratio of peak diastolic to systolic pressure as measured by finger plethysmograph (peak ratio at end of treatment 1.33 vs. 1.09, $p < 0.001$). Table 2 summarizes the details of the treatment and of angina class and nitroglycerin use after treatment. Immediately after treatment course completion, a reduction of CCS angina class was seen in 75.0% of PUMPER vs. 72.7% of non-PUMPER, a nonsignificant difference. Episodes of angina, nitroglycerin use and frequency of nitroglycerin use were reduced substantially in both groups.

Six-month follow-up data were completed for 79.9% of non-PUMPER and 76.7% of PUMPER. Table 3 summarizes the angina characteristics and nitroglycerin use at 6 months. A significant difference was found in the proportion of patients who had maintained their angina reduction. For PUMPER, 89% reported angina that was less than or the same as that immediately post-EECP, and

Table 2. Post-EECP results

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Hours of treatment (mean)	33.8	34.3
Completed treatment, %	82.8	88.8
Diastolic augmentation		
First-hour peak ratio***	0.8 ± 0.5	0.9 ± 0.5
Last-hour peak ratio***	1.1 ± 0.6	1.3 ± 0.6
CCS angina class, %**		
No angina	17.1	35.7
Class I	22.4	27.0
Class II	32.8	21.4
Class III	21.3	11.2
Class IV	7.1	5.6
Angina decreased by one or more classes, %	73.0	74.8
Decrease in angina episodes/week***	7.6 ± 11.6	5.2 ± 9.3
Nitroglycerin use, %	17.4	15.2
Decrease in frequency of nitroglycerin use/week*	7.0 ± 11.0	5.9 ± 10.5

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Results at 6 months after EECP treatment

	Non-PUMPER (n = 4,239)	PUMPER (n = 215)
Completed 6-month follow-up	3,388 (79.9%)	165 (76.7%)
CCS angina class, %**		
No angina	25.1	51.9
Class I	20.8	19.2
Class II	29.8	20.5
Class III	18.2	7.6
Class IV	6.1	0.5
Angina episodes/week***	4.7 ± 7.8	1.9 ± 3.4
Angina same or less than post-EECP, %**	79.4	89.0
Overall success, %[a] ***	77.1	83.9
Nitroglycerin use, %***	45.3	19.5
Frequency of use/week	6.2 ± 8.6	3.4 ± 3.6

[a] Angina reduction from before to after EECP and no worsening at 6 months.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

83.9% reported less angina than they had before EECP. For the non-PUMPER group, the figures were 79.4 and 77.1% ($p < 0.01$ and $p < 0.05$, respectively). Adverse cardiac events occurring both during the treatment period and out to 6 months are shown in table 4. The frequency of major events (death/myocardial infarction/CABG/PCI) during the treatment period was very low for both groups, and although higher during the 6 months' follow-up period (6.3% for PUMPER, 10.8% for non-PUMPER, p = NS) was not significantly different between the two groups. At 6 months, revascularization had been performed in 6.1% of non-PUMPER and 5% of PUMPER. Interestingly, the non-PUMPER group patients were more likely to undergo PCI (4.2 vs. 0.6%, $p < 0.05$) and the PUMPER group was more likely to undergo CABG (4.4 vs. 1.9%, $p < 0.05$) despite the significantly higher prevalence of multivessel coronary artery disease in the non-PUMPER group. There was no significant difference in the revascularization rates at 6 months despite 100% of the PUMPER being candidates for revascularization versus only 16% of the non-PUMPER. At the end of the 6-month follow-up, myocardial infarctions (1.0 vs. 3.3%,

Table 4. Adverse events

	After EECP[1]		During follow-up[2]	
	non-PUMPER	PUMPER	non-PUMPER	PUMPER
Patients, n	4,239	215	3,388	165
Death, %	0.3	0.0	2.9	3.2
Myocardial infarction, %	0.7	0.9	3.3	1.0†
CABG, %	0.2	0.9*	1.9	4.4†
PCI, %	1.0	0.0	4.2	0.6†
Death/MI/CABG/PCI, %	1.9	1.4	10.6	8.0
Any hospitalization, %	–	–	21.9	8.8†††

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ comparing events after EECP.

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ comparing events during follow-up.

[1] Occurring during the period of EECP treatment and up to 5 days after the last day of treatment.

[2] Occurring from the 6th day after treatment to 6 months.

$p < 0.05$) and hospitalizations (8.8 vs. 21.9%, $p < 0.001$) were significantly lower for the PUMPER group; mortality was similar in both groups.

Discussion

Trials comparing medical versus surgical revascularization for coronary artery disease have focused on survival. Surgical revascularization has demonstrated benefit in the patient with three-vessel disease and in one- or two-vessel disease involving the proximal left anterior descending artery. The greatest absolute reduction in mortality is seen in patients with depressed left ventricular function. Those patients with preserved left ventricular function and one- or two-vessel disease not involving the left descending anterior artery would be expected to demonstrate only a marginal survival benefit from CABG. Extensive algorithms have been developed using clinical and angiographic variables to estimate surgical survival benefit, but are consistent with little evidence of benefit in the low-risk (1% annual mortality) patient [14]. Evidence-based survival benefit from angioplasty is even more problematic.

In view of the above, EECP may have a role in the patient who continues to have disabling angina refractory to medical therapy but who, on the basis of limited coronary artery disease and preserved left ventricular function, would not be expected to show a mortality benefit with surgery. It may also have a role in the patient who does not wish to be exposed to the risks of CABG or PCI (e.g., cognitive deficits, stroke, death, perioperative myocardial infarction). Depending on its effectiveness in improving myocardial perfusion, EECP revascularization may also benefit patients in moderate or higher cardiac risk groups. EECP is a noninvasive technique, potentially widely accessible, and robust in its effectiveness in relieving angina.

Though there were initial concerns regarding the potential for exacerbating peripheral arterial insufficiency, precipitating heart failure, and in causing pulmonary emboli, clinical follow-up of over 5,000 patients has shown EECP to be safe and effective. Indeed, EECP has been successfully used in patient groups at increased risk for traditional revascularization (women, elderly including patients >100 years old [15], diabetics [16], end-stage renal disease, depressed left ventricular function [17]).

While the PUMPER group would be expected, from the clinical and angiographic information collected, to have a lower annual cardiac mortality than the non-PUMPER group, they are still largely a moderate-risk group, and as such, they still may not represent the low-risk medically refractory patient who would demonstrate the greatest benefit/risk from EECP. The comparison of the PUMPER and non-PUMPER groups can, however, provide information regarding the relative efficacy, durability and morbidity and mortality of the two groups. While PUMPERs demonstrated a significantly greater hemodynamic effect from EECP during treatment, immediate post-treatment benefits in angina reduction and improvement in angina functional class were similar in both groups. However, at 6 months' follow-up the PUMPER were found to be significantly more likely to maintain or further reduce their angina (fig. 1). While no significant differences were found in major adverse cardiac events

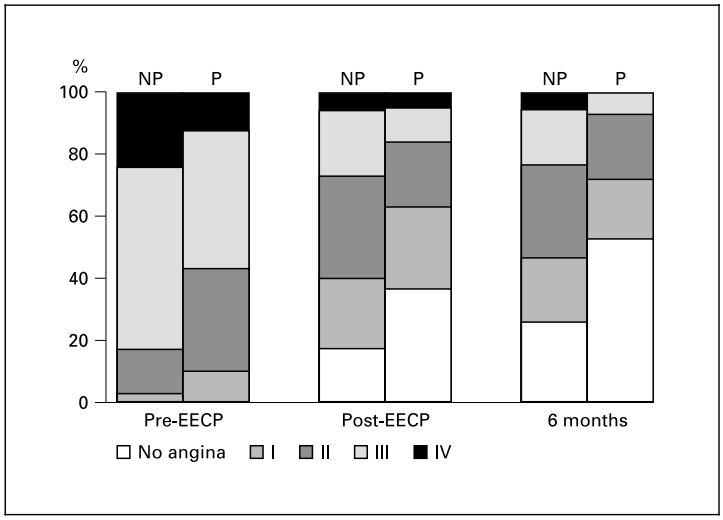

Fig. 1. CCS functional class before EECP, immediately after EECP, and at 6 months after EECP in the non-PUMPER (NP) and PUMPER (P) groups.

between the groups, there were significantly greater and more durable relief of angina, less myocardial infarctions, and fewer hospitalizations in the PUMPER group at 6 months. These findings may support there being a greater success in revascularization in the PUMPER group, which had less extensive coronary disease.

Conclusions

Previously unrevascularized angina patients who are candidates for elective CABG or PCI respond to treatment with EECP with decreased anginal episodes and nitroglycerin use and with improvement in their CCS functional class, similarly to previously revascularized patients. Treatment with EECP resulted in sustained, and often progressive, reduction in angina over the succeeding 6 months. It is interesting to speculate, given the findings of this study, on the proper role of EECP in treating angina patients. Should EECP, a noninvasive therapy, be used as the primary 'revascularization' intervention after medical therapy proves unsatisfactory? Does EECP 'revascularization' alter the risk of cardiac events and mortality sufficiently to justify its use as an alternative in moderate- or high-risk patients? Or should EECP continue to be reserved for patients refractory to medical therapy who are poor candidates for surgical revascularization? While the current study leaves these questions unanswered, it will hopefully promote interest in the appropriately designed study to test these questions. Long-term follow-up will be performed on current study participants to evaluate the duration of benefit and the impact on morbidity, mortality and resource utilization associated with using EECP as the initial treatment for angina.

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The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes

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OBJECTIVES The purpose of this study was to assess safety and efficacy of enhanced external counterpulsation (EECP).

BACKGROUND Case series have shown that EECP can improve exercise tolerance, symptoms and myocardial perfusion in stable angina pectoris.

METHODS A multicenter, prospective, randomized, blinded, controlled trial was conducted in seven university hospitals in 139 outpatients with angina, documented coronary artery disease (CAD) and positive exercise treadmill test. Patients were given 35 h of active counterpulsation (active CP) or inactive counterpulsation (inactive CP) over a four- to seven-week period. Outcome measures were exercise duration and time to ≥1-mm ST-segment depression, average daily anginal attack count and nitroglycerin usage.

RESULTS Exercise duration increased in both groups, but the between-group difference was not significant ($p > 0.3$). Time to ≥1-mm ST-segment depression increased significantly from baseline in active CP compared with inactive CP ($p = 0.01$). More active-CP patients saw a decrease and fewer experienced an increase in angina episodes as compared with inactive-CP patients ($p < 0.05$). Nitroglycerin usage decreased in active CP but did not change in the inactive-CP group. The between-group difference was not significant ($p > 0.7$).

CONCLUSIONS Enhanced external counterpulsation reduces angina and extends time to exercise-induced ischemia in patients with symptomatic CAD. Treatment was relatively well tolerated and free of limiting side effects in most patients. (J Am Coll Cardiol 1999;33:1833–40) © 1999 by the American College of Cardiology

Current treatment for angina, including drug therapy (1) with nitrates, beta-adrenergic blocking agents and calcium channel blocking agents either as single agents or in combination, or revascularization by either percutaneous transluminal coronary angioplasty (2) or coronary artery bypass grafting (CABG) (3), can be effective in a significant number of patients. However, side effects of medications, coronary vasculature not amenable to either initial or repeat revascularization or diminishing treatment benefit may occur over time.

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The search for more therapeutic options for patients with chronic angina has yielded a wide range of new treatment modalities in various stages of clinical evaluation, including transmyocardial laser revascularization (4), minimally invasive bypass surgery (5), spinal cord stimulation (6), transcutaneous electrical nerve stimulation (7) and external counterpulsation (CP) (8).

In the U.S., experience with enhanced external CP (EECP), a modified version of external CP, is based on a series of case studies (9,10) in which EECP was successful in relieving angina, improving exercise tolerance and reducing reversible perfusion defects in radionuclide scans. Despite the use of external CP in its various designs over the

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CP = counterpulsation
EECP = enhanced external counterpulsation
ETT = exercise treadmill test
MI = myocardial infarction
MUST = multicenter study
NO = nitric oxide
NTG = nitroglycerin

past 30 years (11), no controlled trial has been conducted to determine whether the procedure is effective and safe for reducing angina pectoris in patients with coronary artery disease (CAD).

METHODS

Objectives. The multicenter study (MUST)-EECP trial was a randomized, placebo (sham) controlled, multicenter trial designed to evaluate EECP in patients with angina and documented CAD. Treatment effect was determined by comparing changes in exercise treadmill test (ETT) parameters (exercise duration, time to ≥1-mm ST-segment depression), symptoms (frequency of anginal episodes and nitroglycerin [NTG] usage between groups).

Subjects. The MUST-EECP trial was conducted at seven medical centers in the U.S. (see Appendix). Approximately 500 patients with chronic stable angina were considered for inclusion, of whom 139 were randomized between May 1995 and May 1997. Main reasons for nonenrollment included failure to satisfy inclusion/exclusion criteria, and patient refusal. To be eligible, patients had to meet the following criteria: 1) be between 21 and 81 years of age; 2) have symptoms consistent with Canadian Cardiovascular Society Classification angina levels I, II or III; 3) have documented evidence of CAD and 4) have an ETT positive for ischemia.

Evidence of CAD required at least one of the three following criteria: one or more angiographically proved stenosis >70% in at least one major coronary artery; history of myocardial infarction (MI) documented by characteristic creatine kinase elevation and development of Q waves on the electrocardiogram or positive nuclear exercise stress test for MI or ischemia.

Prospective subjects were excluded if they had the following: MI or CABG in the preceding three months, cardiac catheterization in the preceding two weeks, unstable angina, overt congestive heart failure or a left ventricular ejection fraction ≤30%, significant valvular heart disease, blood pressure >180/100 mm Hg, permanent pacemaker or implantable defibrillator, nonbypassed left main stenosis greater than 50%, severe symptomatic peripheral vascular disease, history of varicosities, deep vein thrombosis, phlebitis or stasis ulcer, bleeding diathesis, warfarin use with International Normalized Ratio >2.0, atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering or baseline electrocardiographic abnormalities that would interfere with interpretation of exercise electrocardiogram. Also excluded were pregnant women, women of childbearing potential, subjects unable to undergo treadmill testing and subjects enrolled in a cardiac rehabilitation program or in another research program.

The study was approved by the Institutional Review Boards at participating institutions and conducted in accordance with the Declaration of Helsinki. Enrollment was conditional upon subjects giving written informed consent.

Study organization. The study was coordinated centrally by a Core Laboratory. When an eligible patient was identified at a study center, his or her characteristics were communicated to the Study Coordinator at the Core Laboratory where all eligibility criteria were reviewed. Eligible subjects were assigned at random to receive either active CP or placebo delivered as sham therapy in the form of inactive CP as described below. Treatment allocation was based on random codes generated in blocks of 10, with whole blocks assigned to one center, to ensure that patients were assigned equally to each treatment group at each center (12). The same number of random codes was assigned to each treatment group. Assignment was transmitted only to personnel administering EECP at each study center. Study personnel involved in collecting and processing data at the study centers and at the Core Laboratory remained blinded for the duration of the study. To prevent study subjects from recognizing any observable differences between sham and active treatment, appointments were scheduled so as to minimize any opportunities for study subjects in one group to discuss their experience either with other patients undergoing EECP or with MUST-EECP subjects in the other group. The Study Coordinator at the Core Laboratory was notified of adverse experiences and reported them to an independent data and safety monitoring committee.

Study design. Before randomization, medical history, physical examination and a baseline ETT were performed. The baseline ETT used a standard or a modified Bruce protocol and was performed within four weeks of treatment initiation. All medications (except on-demand NTG) remained unchanged for the duration of the study. Once randomized, patients underwent 35 h of either active CP or inactive CP. Treatment sessions, each lasting 1 h, could be given once or twice per day. At each treatment session, vital signs were recorded, lower extremities were examined for areas of redness or ecchymosis, adverse experiences were reported and study subjects reported the number of anginal episodes experienced and NTG tablets taken during the preceding 24-h period. An adverse reaction was defined as the development of any new symptom or complaint from the time of randomization. Within one week after completion of 35 treatment sessions, a posttreatment ETT was

performed. Baseline and posttreatment ETT were performed by personnel not aware whether the patient was in the active-CP or the inactive-CP group.

Enhanced external counterpulsation. Enhanced external counterpulsation equipment was supplied by the manufacturer, Vasomedical (Westbury, New York). The equipment consists of an air compressor, a console, a treatment table and two sets of three cuffs. Before a treatment session, these cuffs are wrapped around the patient's legs, one set on each leg. Using compressed air, pressure is applied via the cuffs to the patient's lower extremities in a sequence synchronized with the cardiac cycle. In early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs to propel blood back to the heart. This results in an increase of arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation). At end-diastole, air is released instantaneously from all the cuffs to remove the externally applied pressure, allowing the compressed vessels to reconform, thereby reducing vascular impedance. The pressures that can be applied to the cuffs range from 0 to 350 mm Hg. In MUST-EECP, the pressure applied to the cuffs was 300 mm Hg in the active-CP group and 75 mm Hg in the control group, enough to preserve the appearance and feel of an EECP application, but insufficient to alter measurably the patient's blood pressure. Blood pressure changes are monitored by finger plethysmography. To assess the hemodynamic effect of EECP, two ratios are computed electronically, using the systolic and diastolic peak pressures or the area under the systolic and diastolic curves. Ratios greater than one correspond to diastolic values greater than systolic values. In MUST-EECP, the means of patients' diastolic to systolic pressure and area under the curve ratios achieved were 1.41 ± 0.51 (mean $\pm$ SD) and 1.59 ± 0.6, respectively, in active CP, showing effective diastolic augmentation. Changes in these parameters were undetectable in inactive CP, confirming the lack of hemodynamic effect in the latter group. All other aspects of treatment delivery were the same in both groups.

End points. Tracings of each ETT from each study center were sent to the Core Laboratory where exercise duration (s) and time to $\geq$1-mm ST-segment depression (s) were recorded by personnel unaware of the treatment assignment of each patient and whether the ETT was baseline or posttreatment. Exercise duration was defined as elapsed time from the initiation of exercise to the beginning of the recovery period. Time to ST-segment depression was defined as the elapsed time from initiation of exercise to the occurrence of horizontal or down-sloping ST-segment depression $\geq$1 mm, 80 ms after the J point, persisting for at least three consecutive beats.

The average frequency of angina episodes per day (angina counts) was computed by dividing the total number of angina episodes reported at three successive treatment sessions by the number of days in which the sessions took place. Whenever two sessions were conducted on the same day, only angina episodes reported for the first session were used, because the second session covered the same 24-h period as the first session of that day. The first three sessions (i.e., sessions 1 to 3) were considered as the baseline period. In addition, the difference in angina counts between baseline and at end-treatment were calculated as percentage change for each patient in the active- and inactive-CP groups and were classified into the following categories: 50%+ improvement, 25% to 49% improvement, 0 to 24% improvement, 1% to 25% worsening, 26% to 50% worsening, 51% to 100% worsening and >100% worsening. Patients with no episodes at the first three sessions were considered as having no change (0%) if they also had no episodes at other periods, and were considered as worsening by 100% or more if they had episodes at other periods.

Statistical analyses. On the basis of a between-patient standard deviation of 87 s in exercise duration, there was 80% power to detect a 45-s difference in exercise duration between the two study groups using a two-sided test with a 0.05 level of significance. The primary efficacy analyses for ETT parameters were performed on an observed case basis using the intention to treat population. Changes in exercise duration and time to $\geq$1-mm ST-segment depression from baseline to posttreatment ETT were calculated for each subject and compared between treatment groups. An analysis of variance with treatment group as a main effect and treatment site as a blocking factor was then made. The method used for computing angina counts took into account the varying total treatment time among patients many of whom, for the sake of convenience, underwent two treatment sessions daily for at least part of the treatment course (see End Point section). Two analyses of angina counts were performed. An analysis of variance, on rank transformed data by treatment center, was applied to changes in angina counts from baseline to follow-up. Also, the difference between the two treatment groups with respect to percentage change in angina counts was computed for the entire intention to treat population (all randomized patients) and for those patients with $\geq$34 sessions (i.e., for patients having completed EECP treatment). The difference between the two treatment groups with respect to the percent change in each parameter was tested using a Cochran-Mantel-Haenszel chi-square test for ordered categories, stratified by treatment center. Results are presented as adjusted means (least-squares), calculated to accommodate any imbalance in the number of patients in each group among treatment centers. This conforms to the analysis of variance model using treatment center as a blocking factor. The analysis of average usage of on-demand NTG tablets per day (NTG count) was conducted in the same manner as for the analysis of angina counts.

Adverse experiences. The number of patients reporting adverse events was compared between groups using a

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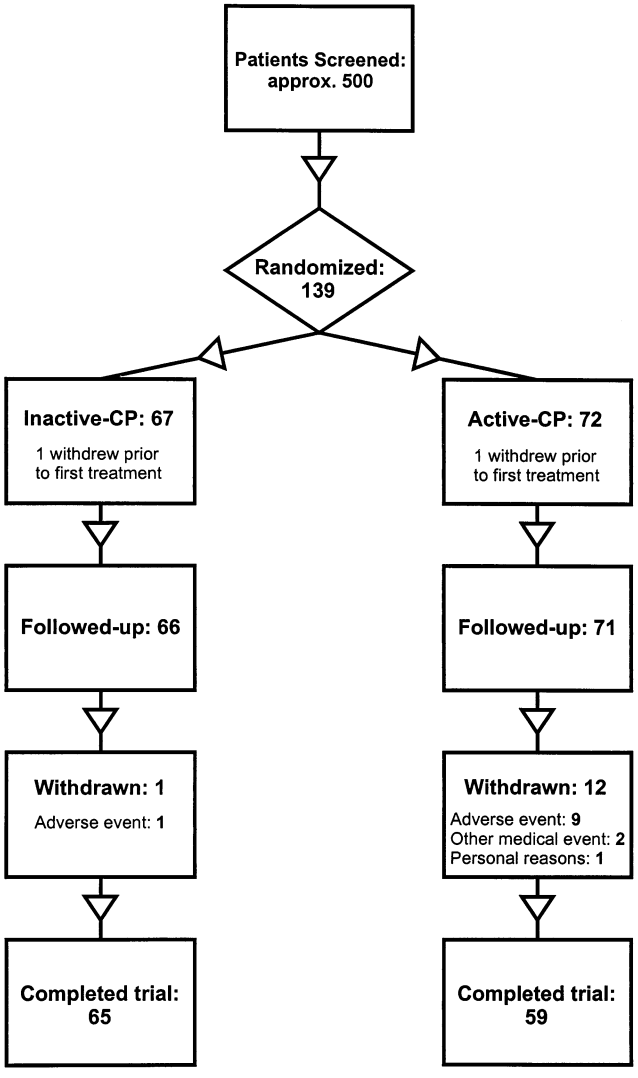

Figure 1. Patient disposition. CP = counterpulsation.

Table 1. Patient Characteristics

	Inactive CP	Active CP	p Values
n	66	71	
Age (mean ± SD)	62 ± 9 yr	64 ± 9 yr	> 0.1
Male	58 (87.9%)	61 (85.9%)	> 0.8
Race			> 0.5
White	49 (74.2%)	55 (77.5%)	
Black	2 (3.0%)	3 (4.2%)	
Hispanic	10 (15.2%)	5 (7.0%)	
Asian	3 (4.5%)	5 (7.0%)	
Other	2 (3.0%)	3 (4.2%)	
CV history			
CCSC			> 0.9
I	17 (25.8%)	19 (26.8%)	
II	34 (51.5%)	35 (49.3%)	
III	15 (22.7%)	17 (23.9%)	
Angina years (mean ± SD)	4.5 ± 4.06	8.56 ± 7.88	< 0.01
Previous MI	27 (40.9%)	40 (56.3%)	< 0.05
Previous CABG	25 (37.9%)	33 (46.5%)	> 0.3
Previous PTCA	22 (33.3%)	27 (38.0%)	> 0.5
Residual vessel disease			> 0.1
0	5 (7.6%)	5 (7.0%)	
1	23 (34.8%)	21 (29.6%)	
2	17 (15.8%)	19 (26.8%)	
3	9 (13.6%)	21 (29.6%)	
No data	12 (18.2%)	5 (7.0%)	
CV medications			> 0.8
Nitrates	54 (81.8%)	56 (78.9%)	
ASA	60 (90.9%)	32 (87.3%)	
CCB	36 (54.5%)	44 (62.0%)	
BB	51 (77.3%)	50 (70.4%)	
Lipid-lowering agents	33 (50.0%)	44 (62.0%)	

Angina years = years since diagnosis; ASA = acetylsalicylic acid taken as an antithrombotic; BB = beta-blocker; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CCSC = Canadian Cardiovascular Society functional classification for angina; CP = counterpulsation; CV = cardiovascular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

chi-square test. A chi-square test was also used to compare the number of sessions where leg discomfort was reported.

RESULTS

Patient enrollment. One hundred thirty-nine patients were randomized in MUST-EECP. Patient disposition is shown in Figure 1.

Exercise duration data were available for 57 subjects in the active-CP and 58 in the inactive-CP group. Fourteen subjects in active CP were not evaluable for exercise duration: 4 had protocol violations, 7 withdrew because of adverse experiences and 3 dropped out for personal reasons. In the inactive-CP group, 8 subjects were not evaluable for exercise duration. Seven of these had protocol violations, and one dropped out because of an adverse experience. Evaluable data for time to ≥1-mm ST-segment depression were available for 56 subjects in each study group. Digoxin use invalidated time to ST-segment depression analysis in one subject in the active-CP group and two in the inactive-CP group.

Patient characteristics. The characteristics of the randomized groups were similar, although a higher percentage of patients in the active-CP group had a history of previous MI and suffered from angina for a longer period of time (Table 1). Antianginal treatment was similar for both groups (Table 1). More than 70% of patients in each group had Canadian Cardiovascular Society Classification class II or III and over 70% of each group had undergone prior CABG or angioplasty.

Efficacy. EXERCISE TREADMILL TEST. Exercise duration was 426 ± 20 s at baseline and 470 ± 20 s posttreatment in the active-CP group. In the inactive-CP group, exercise

Table 2. Exercise Treadmill Test

	Inactive CP				Active CP				Between-Group p Value
	n	Pre-CP	Post-CP	p Value	n	Pre-CP	Post-CP	p Value	
Exercise duration (s)	58	432 ± 22	464 ± 22	< 0.03	57	426 ± 20	470 ± 20	< 0.001	< 0.31
Time to ≥1-mm ST-segment depression (s)	56	326 ± 21	330 ± 20	< 0.74	56	337 ± 18	379 ± 18	< 0.002	= 0.01

Duration in seconds, mean ± SEM.
Pre-CP: baseline, before counterpulsation; Post-CP: follow-up, postcounterpulsation. p values are computed based on adjusted change in duration from baseline to follow-up.

duration was 432 ± 22 s at baseline and 464 ± 22 s posttreatment (Table 2). There was no significant difference between groups in change in exercise duration from baseline to posttreatment (adjusted mean: active CP: 42 ± 11 s vs. inactive CP: 26 ± 12 s; $p > 0.3$).

Time to ≥1-mm ST-segment depression was 337 ± 18 s at baseline and 379 ± 18 s posttreatment in the active-CP group. In the inactive-CP group, time to ≥1-mm ST-segment depression was 326 ± 21 s at baseline and 330 ± 20 s posttreatment (Table 2). There was a significant difference between groups in the change in time to exercise-induced ischemia from baseline to posttreatment (adjusted mean: active CP: 37 ± 11 s vs. inactive CP: −4 ± 12 s; $p = 0.01$).

ANGINA COUNTS. In the intention to treat analysis, angina counts were 0.76 ± 0.15 at baseline and 0.55 ± 0.27 posttreatment in the active-CP group. In the inactive-CP group, angina counts were 0.76 ± 0.13 at baseline and 0.77 ± 0.2 posttreatment. The difference between groups in the change in angina counts from baseline to posttreatment showed a trend to statistical significance (adjusted mean: active CP: −0.11 ± 0.21 vs. inactive CP: 0.13 ± 0.22; $p < 0.09$). In patients who completed ≥34 sessions, angina counts were 0.72 ± 0.14 at baseline and 0.57 ± 0.38 posttreatment in the active-CP group. In the inactive-CP group, angina counts were 0.77 ± 0.14 at baseline and 0.76 ± 0.22 posttreatment. The difference between groups in the change in angina counts from baseline was statistically significant (adjusted mean: active CP: −0.033 ± 0.27 vs. inactive CP: 0.15 ± 0.27; $p < 0.035$). A similar number of patients in each group showed a 0 to 25% level of improvement, but more patients reported a >50% improvement in angina frequency, and fewer worsened in the active-CP group compared with the inactive-CP group ($p < 0.05$, Table 3).

NITROGLYCERIN USAGE. In the intention to treat analysis, NTG usage was 0.47 ± 0.13 at baseline and 0.19 ± 0.07 posttreatment in the active-CP group. In the inactive-CP group, NTG usage was 0.51 ± 0.15 at baseline and 0.45 ± 0.19 posttreatment. The difference between groups in change in NTG usage from baseline to posttreatment was not significant (adjusted mean: active CP: −0.32 ± 0.12 vs. inactive CP: −0.10 ± 0.12; $p > 0.1$). In patients who completed ≥34 sessions, NTG usage was 0.39 ± 0.11 at baseline and 0.12 ± 0.04 posttreatment in the active-CP group. In the inactive-CP group, NTG usage was 0.56 ± 0.17 at baseline and 0.43 ± 0.21 posttreatment. The difference between groups in this parameter from baseline to posttreatment was not significant (adjusted mean: active CP: −0.32 ± 0.15 vs. inactive CP: −0.19 ± 0.14; $p > 0.1$).

ADVERSE EXPERIENCES. Both treatment groups, in response to queries, reported a relatively high incidence of adverse events at each treatment session. This is not surprising, because patients were questioned daily by research nurses about any adverse reaction experienced since the previous session. More patients in the active-CP group reported adverse events than in the inactive-CP group: 39 (55%) versus 17 (26%), $p < 0.001$. Ten of the 25 events reported by the 17 patients in the inactive-CP group were considered device-related, involving either the skin, lower legs or back. Thirty-seven of the 70 events reported by the 39 patients in the active-CP group were considered device-

Table 3. Angina Counts

			Improvement			Worsening				p Value
		Median	50+%	25%–49%	0%–24%	1%–25%	26%–50%	51%–100%	100+%	
Intention to treat										
Inactive CP	66	0%	21	3	28	2	2	4	6	
Active CP	71	−20%	32	1	33	0	0	2	3	< 0.05
≥34 sessions										
Inactive CP	59	0%	19	2	24	0	2	5	7	
Active CP	57	−50%	29	1	23	0	0	0	4	< 0.02

Categories of change are expressed in percent versus baseline. Daily average of self-reported episodes of angina pectoris are computed over three 24-h periods. p values are calculated for between-group differences using a Cochran-Mantel-Haenszel chi-square test for ordered categories stratified by treatment center.

Table 4. Adverse Experiences

	Inactive CP (n = 66)	Active CP (n = 71)	
	n (%)	n (%)	p Value
Patients with AE	17 (25.8)	39 (54.9)	< 0.001
Adverse experiences—non–device related			
Viral syndrome	0	1	> 0.5
Anxiety	0	2	= 0.5
Dizziness	1	3	> 0.5
Tinnitus	0	1	> 0.5
GI disturbances	1	1	> 0.5
Headache	0	1	> 0.5
Blood pressure change	1	1	> 0.5
Epistaxis	0	2	= 0.5
Angina	1	1	> 0.5
Other chest pain	3	7	= 0.3
A/V arrhythmia	3	9	> 0.2
Heart rate change (sinusal)	3	0	= 0.1
Respiratory	2	4	> 0.5
Total	15	33	< 0.005
Adverse experiences—device related			
Paresthesia	1	2	> 0.5
Edema, swelling	0	2	= 0.5
Skin abrasion, bruise, blister	2	13	= 0.005
Pain (legs, back)	7	20	= 0.01
Total	10	37	< 0.001

Some patients reported more than one adverse experience (AE), hence total AE exceed numbers of patients reporting AE. p value: Fisher exact test.
A/V = atrioventricular; CP = counterpulsation; GI = gastrointestinal.

related. The remaining complaints in each group were considered minor and not directly related to treatment (Table 4). Leg discomfort was reported in 11.6 ± 22.7% of active-CP sessions and 4.9 ± 18.7% of active-CP sessions (p = 0.06). Although 47 of the 95 events reported by both groups combined were considered device-related, only five patients withdrew from the study due to leg complaints (e.g., pain, abrasion).

DISCUSSION

Effect on exercise treadmill test. The MUST-EECP trial confirms that EECP can reduce exercise-induced ischemia in patients with symptomatic CAD. The lack of a significant treatment effect on exercise duration despite reduction in other measures of ischemia has been seen in other clinical trials involving antianginal agents (13,14). Training effect or the fact that most study patients were limited by nonanginal symptoms such as fatigue or shortness of breath on the treadmill tests may have produced a fixed exercise duration and account for this observation. Moreover, EECP might be less likely to extend exercise capacity when added to background treatments of antianginal drugs and coronary revascularization than if such treatments were not in place. There was, however, an increase in time to exercise-induced ischemia, a more objective parameter of treatment effect, in the active-CP group, and the between-group difference was significant.

Effect on angina counts and NTG usage. A trend in angina reduction with EECP was seen in the intention to treat analysis and became significant when the analysis included only those subjects completing at least 34 sessions. This observation suggests that a certain number of treatment hours are required to maximize the antianginal benefit of this device (see Mechanisms of Action section). Although NTG usage dropped in the active-CP group, no between-group difference was noted. The wide range of NTG tablets taken by both groups and the common practice of patients with this degree of angina of taking NTG prophylactically, a habit unlikely to be changed over the course of a seven-week study, may explain this finding.

Mechanisms of action. The mechanisms underlying the effects of EECP have been under investigation for many years. Acute hemodynamic improvement simulating the effects of intra-aortic balloon CP can be achieved (15), and a multicenter randomized trial in patients with acute MI and heart failure demonstrated that external CP reduced morbidity and mortality (16). The use of this early device to treat angina also suggested benefit (17,18), but variations in treatment protocol produced variable results.

Reasons for continued relief of angina beyond the acute hemodynamic beneficial effects of EECP treatment as described in case series (8–10) are unclear. Increased transmyocardial pressure gradients for the prescribed 35 sessions could open collaterals (19,20). Chronic exposure of the coronary and peripheral arterial bed to the augmented blood flow and increased shear forces produced by EECP could lead to increased endothelial cell production of nitric oxide (NO) and prostacyclin, powerful mediators of vasodilation. Supporting this notion is the recent observation that sustained exercise in dogs increased endothelial NO synthase gene expression and coronary vascular NO production (21). Increased blood flow may regulate the elaboration of a variety of paracrine substances that participate in vascular remodeling and reactivity (22). Consistent with these hypotheses, other strategies targeted to improve endothelial-dependent vasodilation, such as estrogen replacement in postmenopausal women (23) and low density lipoprotein lowering in hypercholesterolemic patients (24), have also been shown to decrease ischemia.

Clinical implications. Because coronary disease is a chronic condition, and long-term survival is extended with secondary prevention, practitioners see patients with recurrent angina despite therapy with anti-ischemic agents and coronary revascularization. Most patients enrolled in MUST-EECP fall into this category. In addition, there are many patients who are inoperable, at high risk for operative

complications or postoperative failure, whose coronary anatomy is not readily amenable to invasive procedures or who have comorbid states associated with excessive risk. For such patients, EECP could extend the range of treatment options.

Limitations. The design of MUST-EECP has several limitations. The use of a sham method to serve as a placebo control is imperfect but is used often in device- or procedure-related clinical trials (25,26). The fact that some patients in the sham-treated group reported lower leg and skin adverse reactions suggests that sham CP simulated active treatment as intended. Although care was taken to prevent study participants from witnessing other patients receiving EECP, it is possible that some patients in MUST-EECP guessed correctly their form of treatment. Furthermore, it was impossible to blind personnel applying the EECP treatment, leaving open the possibility that the form of treatment could have been suggested inadvertently. Although angina counts and NTG usage were assessed using the subjects' recollection, patients were only asked to recall whether these events had occurred in the 24-h period preceding each treatment session. Most treatments for angina have been the subject of cost-effectiveness analyses and, at the present time, no such data are available for EECP. In addition, MUST-EECP examines only the immediate effect of treatment. Its long-term effects on symptoms and clinical events are not known.

Conclusions. The MUST-EECP trial, the first randomized controlled study to evaluate EECP, indicates that enhanced external CP can reduce angina and extend the time to ischemia on ETT in patients with symptomatic CAD. The treatment was relatively well tolerated and free of limiting side effects in most patients.

APPENDIX

MUST-EECP Study Centers

Columbia-Presbyterian Medical Center, Columbia University (New York, New York); Moffit-Long Hospital, University of California at San Francisco (San Francisco, California); Yale University School of Medicine (New Haven, Connecticut); Beth Israel Deaconess Medical Center, Harvard University (Boston, Massachusetts); Grant/Riverside Methodist Hospitals (Columbus, Ohio); Presbyterian University Hospital, University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania); and Loyola University Medical Center (Maywood, Illinois).

MUST-EECP Trial Coordinators

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MUST-EECP Organization

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Long-Term Prognosis of Patients with Angina Treated with Enhanced External Counterpulsation: Five-Year Follow-Up Study

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Summary

Background: Enhanced external counterpulsation (EECP) is a noninvasive treatment for coronary artery disease (CAD) that has been used successfully in patients not responding to medical and/or surgical therapy.

Hypothesis: The study was undertaken to evaluate the effect of EECP on long-term prognosis in such patients.

Methods: Major adverse cardiovascular events (MACE) were tracked in 33 patients with CAD treated with EECP. Patients were subgrouped based on whether or not they demonstrated an early improvement in radionuclide stress perfusion imaging (Responders vs. Nonresponders) and followed for MACE over a mean follow-up of 5 years. Patient population characteristics included 73% with multivessel disease; 45% with prior myocardial infarction(s); and 61% who had undergone either coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), or both.

Results: There were 26 of 33 (79%) Responders, and 7 of 33 (21%) Nonresponders. Subsequent MACE over the 5-year follow-up included four deaths and eight patients with cardiovascular events [acute myocardial infarct (4), new CABG or PTCA (6), valve replacement (1), unstable angina (1)]. Nonresponders had significantly ($p < 0.01$) more MACE (6/7 or 86%) than Responders (6/26 or 23%). Overall, 21 of the 33 (64%) patients remained alive and without MACE and the need for revascularization 5 years post EECP treatment

Conclusion: This study suggests that, particularly for the majority of patients demonstrating improvement in radionuclide stress perfusion post treatment, EECP may be an effective long-term therapy.

Key words: coronary artery disease, external counterpulsation, prognosis

Introduction

The concept that coronary blood flow could be increased by 20–40% by raising diastolic perfusion pressure was proposed by Kantrowitz and Kantrowitz in 1953.[1] Enhanced external counterpulsation (EECP) applies external pressure to the lower extremities in a timed, sequential manner, using three pairs of pneumatic cuffs, to produce effective diastolic augmentation (Fig. 1). The sequential inflation of pressure cuffs "milks" blood from the vasculature of the legs and is more effective in producing diastolic augmentation and increasing venous return than the earlier one-chamber hydraulic counterpulsation system. The mechanism of action is similar to that of the intraaortic balloon pump (IABP) in producing timed diastolic augmentation. By also augmenting venous return, EECP may further increase cardiac output.

Studies using radionuclide stress testing have documented improved myocardial perfusion, exercise tolerance, and decreased angina following EECP treatment in about 80% of subjects.[3,4] Improvement based on stress myocardial perfusion imaging has been shown to be related to the extent of coronary artery disease (CAD) and prior revascularization.[5,6] The presence of a patent conduit (native coronary or bypass graft) increases the likelihood of a favorable response and has been termed "the patent vessel hypothesis." This is in concert with the demonstration by Kern *et al.* that augmented diastolic pressures and flow generated by the IABP are only effectively transmitted to the distal coronary vasculature in the absence of a significant intervening coronary stenosis.[7,8] Diastolic augmentation increases the diastolic transmyocardial pressure gradient at a time when coronary flow impedance is low, thereby maximizing coronary blood flow and perhaps facilitating development or recruitment of collaterals.

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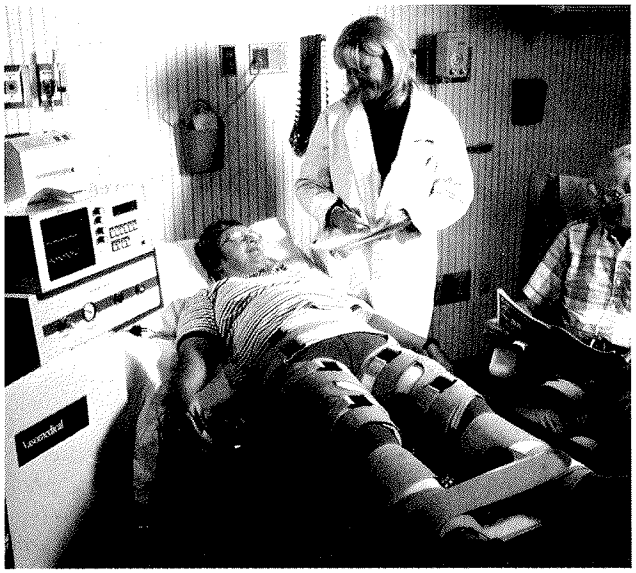

FIG. 1 The enhanced external counterpulsation device used in treating patients with coronary artery disease consists of a control console, a treatment table, three pairs of cuffs wrapped around the lower extremities, and a compressor unit (not shown).

The initial improvement in stress myocardial imaging following EECP has been shown to be maintained in a majority of treated patients over a 3-year follow-up period.[9] The present study was planned to determine whether there was evidence for a sustained clinical benefit from EECP by assessing major adverse cardiovascular events (MACE) over a 5-year post-treatment period. Significant MACE chosen as endpoints included death, myocardial infarction, revascularization [coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)], and cardiac related hospitalization.

Methods

A cohort of consecutive patients with angina treated with EECP from 1989 to 1991 was followed for a mean of 5 years (range 4–7 years). The study protocol and patient informed consent had been approved by the institutional review board of the State University of New York at Stony Brook. When first treated with EECP, the patients had stable but limiting angina pectoris despite medical and/or revascularization therapy (CABG or PTCA). A radionuclide stress test demonstrating reversible perfusion defects consistent with ischemia was also required prior to EECP treatment. The patients received an initial 35–36 h course of EECP administered at 1–2 h daily sessions for 5 days a week and were followed for a mean of 5 years for MACE.

Radionuclide stress tests were performed pre and post initial EECP treatments to the same cardiac work load and double product. The radionuclide stress tests were interpreted in a blinded fashion by two trained readers without knowledge of the patients or of their clinical status. Based on the post-EECP stress radionuclide perfusion imaging, two subgroups were identified: (1) Responders—those patients demonstrating a decrease in the size or number of radionuclide stress perfusion defects post EECP, and (2) Nonresponders—those patients without evidence of radionuclide perfusion defect improvement. Differences pre and post treatment and between these groups were analyzed using the chi-square test, with significance assumed at the $p < 0.05$ level. Multifactorial analysis of patient baseline characteristics predicting a favorable response to EECP treatment was also performed, with significance assumed at the $p < 0.05$ level.

No risk factor modification was attempted post EECP treatment other than that which may have been initiated by the patient or the patient's physician. Follow-up treatment decisions were made by the patient and physician and included additional EECP treatments for some patients.

Exclusions for treatment included decompensated heart failure, aortic valve insufficiency, myocardial infarction within the prior 3 months or unstable angina, severe peripheral vascular disease (occlusive arterial disease or thrombophlebitis), arrhythmias interfering with timing (atrial fibrillation, frequent ectopy, pacemakers), uncontrolled hypertension (blood pressure > 180/110 mmHg), significant bleeding diathesis.

Initial Results

There were 33 patients enrolled in this study. The mean age of the patients was 61.4 years (range 45–74 years); 31 patients were men and 2 were women. Cardiac angiography prior to entry had been performed in 30 of the 33 patients, with 73% patients having multivessel disease; 45% of patients had prior myocardial infarction(s), and 61% of patients had prior revascularization procedures (50 total revascularization procedures: 17 prior CABG in 12 patients, 33 prior PTCA in 15 patients; 7 patients with prior PTCA and CABG) (Table I).

TABLE I Patient characteristics: All treated patients, Responder and Nonresponder subgroups (by initial improvement in radionuclide stress test)

	All patients	Responders	Non-responders	Significance
Age	61.4 ± 9.5	69.8 ± 9.4	67.3 ± 8.2	p = NS
Male sex (%)	31/33 (94)	25/26 (96)	6/7 (86)	p = NS
Diabetes (%)	6/33 (18)	3/26 (12)	3/7 (43)	p = < 0.20
Single-VD (%)	8/30 (27)	8/25 (32)	0/5 (0)	p = < 0.30
Multi-VD (%)	22/30 (73)	17/25 (68)	5/5 (100)	p = < 0.30
Prior MI (%)	15/33 (45)	11/26 (42)	4/7 (57)	p = NS
Prior revasc (%)	20/33 (61)	16/26 (62)	4/7 (57)	p = NS

Abbreviations: Single-VD = single-vessel disease, multi-VD = multivessel disease, MI = myocardial infarction, revasc = revascularization (CABG or PTCA), NS = not significant.

TABLE II Early enhanced external counterpulsation (EECP) effect on antianginal therapy: All treated patients, Responder and Non-Responder subgroups (by initial improvement in post EECP radionuclide stress test)

Antianginal treatment	All patients (n = 33)		Responders (n = 26)		Nonresponders (n = 7)	
	Pre EECP	Post EECP	Pre EECP	Post EECP	Pre EECP	Post EECP
LA nitrates	15	12	10	9	5	3
Beta blockers	15	13	12	10	3	3
Calcium CB	28	26	23	21	5	5
> 1 Less antianginal post Rx	11		8		3	
> 1 More antianginal post Rx	2		1		1	

Abbreviations: Rx = EECP treatment, LA nitrates = Long-acting nitrates, Calcium-CB = calcium-channel blockers.

Enhanced external counterpulsation was well tolerated, with all patients completing the course of therapy. As reported by patients, anginal symptoms (frequency, severity, ease of precipitation, and duration of episodes) decreased in all patients. Antianginal medications at baseline and the effect of EECP treatment are shown in Table II. Post therapy, long acting nitrate use decreased by 20%, beta-blocker use decreased by 13%, calcium-channel blocker use decreased by 7%. Eleven patients (33%) were able to take one or more less antianginal medications post EECP treatment; only two patients (6%) took an additional antianginal medication post treatment.

Radionuclide stress tests performed to the same cardiac work load and double product pre and post initial EECP treatment demonstrated a significant ($p < 0.01$) improvement in perfusion defects in 26 of 33 (79%) patients (Responders). Stress perfusion defects in the remaining seven patients were unchanged post treatment (Nonresponders). It is interesting to note that the improvement in early post EECP stress perfusion did not correlate with change in daily medication use. A decrease in antianginal medication use was seen in 31% of the Responders and in 43% of the Nonresponders (p = NS).

All of the EECP Nonresponders with known angiographic anatomy had multivessel coronary disease and all of the patients with single-vessel coronary disease with known angiographic anatomy (8/8) were Responders to EECP treatment. This was not, however, a statistically significant difference (p = NS). Prior revascularization with PTCA or CABG was also not predictive of response to EECP therapy (p= NS). Baseline characteristics of the Nonresponder group showed them to be older, more likely to be female, and with a higher prevalence of diabetes; none of these differences from the Responder group reached statistical significance (Table I).

Late Results

Over the course of the mean follow-up of 5 years, 13 of 33 (39%) patients underwent additional treatment with EECP (causing the cumulative mean hours of EECP administered for the entire group to rise to 55.7 h over the follow-up period (49.75 h in the Responders and 77.8 h in the Nonresponders). The reasons for additional EECP treatment included worsening or recurrent angina, persistent ischemic defects on radionuclide stress perfusion imaging, "tune ups" (with no objective or subjective evidence of worsening of the patient's condition).

During the follow-up period four patients died and nine patients experienced interim events (Fig. 2). The causes and the timing of the deaths were diverse: one patient died of cardiac arrest 1 year after EECP treatment, a second patient died at 3 years as a complication of angioplasty, a third patient died of congestive heart failure at 3 years, and the fourth death occurred during sleep 6 years after EECP therapy. Interim events requiring hospitalization occurred in eight additional patients and included acute myocardial infarction in three, revascularization procedures in five, aortic valve replacement in one, and unstable angina in one patient.

Mortality or MACE occurred in 6 of 7 patients (86%) of the Nonresponder group. In comparison, significantly fewer, 6 of 26 patients (23%) in the Responder group, reached endpoints ($p < 0.01$). Overall, 21 of the 33 (64%) EECP-treated patients remained alive 5 years after therapy without cardiovascular morbidity or need for repeat revascularization.

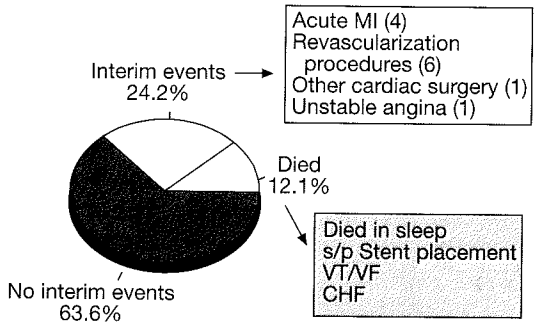

FIG. 2 Graphic representation of the proportion and cause(s) of mortality and cardiovascular morbidity post enhanced external counterpulsation in 33 patients with angina at 5-year follow-up. MI = myocardial infarction, VT = ventricular tachycardia, VF = ventricular fibrillation, CHF = congestive heart failure.

Discussion

Enhanced external counterpulsation has been useful in treating angina, improving exercise tolerance, and decreasing radionuclide stress perfusion defects in about 80% of patients.[3–5] In the recently reported Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial, a prospective, randomized, blinded study of EECP, treatment demonstrated a significant increase in time to ST-segment depression on treadmill exercise testing, a decrease in antianginal medication usage, and sustained quality of life benefits by psychometric testing.[10, 11]

The studied cohort is a population of consecutively treated patients with angina and with predominant multivessel CAD and persistent provokable ischemia despite medications and/or prior revascularization. The patients were followed for a mean of 5 years, with the objective of providing information on the effect of EECP treatment on subsequent major adverse cardiovascular events, including the need for hospitalization and repeat revascularization. The sample size is small, predominately male, and from a single center. While not a primary objective of the study, the size of the sample may have particularly influenced the ability to detect pretreatment patient characteristics predicting a response to therapy. This is probably true of the effect of multivessel disease on response to therapy, where a larger study cohort showed a significant relation between scintigraphic improvement after EECP and extent of disease.[5] While a single center favorably influences procedural consistency, it also introduces bias and is less robust than a multicenter study, which has a broad cross section of providers and patient populations to draw on. The findings of this pilot study warrant confirmation in a larger, blinded, randomized multicenter trial.

The marked difference in MACE noted between the patients demonstrating improvement in their stress radionuclide imaging (79%) and those patients who failed to demonstrate objective improvement with treatment supports a true treatment effect of EECP (Fig. 3). Mortality and cardiovascular morbidity were significantly increased in the group of 7 patients in whom objective improvement was not demonstrable (Nonresponders) in comparison with the group of 26 patients demonstrating improvement in radionuclide stress perfusion imaging (Responders). If the primary effect of EECP was that of a placebo, neither an improvement in radionuclide perfusion nor differences in the frequency of MACE between Responding and Nonresponding patient groups would be expected. By contrast, the immediate effect on use of long-acting antianginals after treatment is similar in both Responder and Nonresponder groups and is probably a placebo effect.

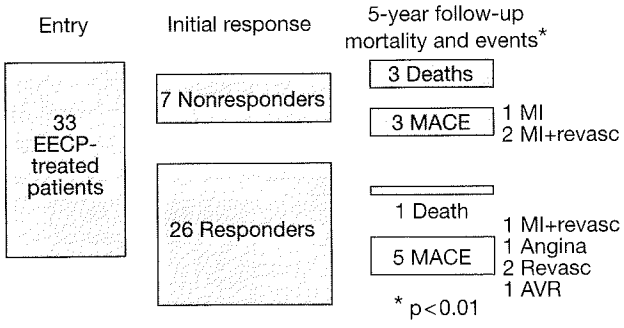

FIG. 3 Effect of initial response to enhanced external counterpulsation (EECP) on subsequent mortality and major adverse cardiovascular events (MACE). MI = myocardial infarction, revasc = revascularization, MACE = major adverse cardiovascular event, AVR = aortic valve replacement.

The 5-year survival of EECP-treated patients was 88%, which is similar to mortality rates reported in contemporary medical and revascularization (CABG or PTCA) trials such as the Coronary Artery Surgery Study (CASS),[12] the CABG meta-analysis,[13] and the Bypass Angioplasty Revascularization Investigation (BARI) (Table III).[14] The patient characteristics of our cohort were similar to those in patients in these trials who had multivessel disease, mean left ventricular ejection fraction of about 50%, and previous myocardial infarction rates of 30–50%. Unlike patients in these groups, most of the patients treated with EECP had had prior PTCA and/or CABG. As this is a historical comparison, it is unclear whether this result could be expected from a randomized trial.

When mortality is considered together with the interim rate of nonfatal events in 8 of the 33 (24%) treated patients, 21 of the 33 (64%) EECP-treated patients remained alive and free of MACE, including the need for revascularization, over a follow-up period of 5 years.

Conclusion

Previous studies have demonstrated that EECP improves myocardial stress perfusion in about 80% of patients, with the

TABLE III Comparison of 5-year survival rates for enhanced external counterpulsation (EECP) versus reported medical and surgical trials

Ref. No.	Study	5-Year survival
	EECP	88%
12	CASS—medical treatment	78%
13	CABG meta-analysis (medical)	84%
	(CABG)	90%
14	BARI—PTCA	86%
	—CABG	89%

EECP patient characteristics were similar to most of those patients having multivessel disease, mean LVEF about 50%, and previous MI rate 30–50%. However, many of the EECP patients also had prior PTCA and/or CABG.

Abbreviations: CASS = Coronary Artery Surgery Study, CABG meta-analysis = Coronary Artery Bypass Graft Surgery Trialists Collaboration, BARI = Bypass Angioplasty Revascularization Investigation, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting.

benefit sustained in a majority of treated patients over a 3-year follow-up.

The present study focuses on outcomes of mortality and major adverse cardiovascular events in an expanded cohort with a 5-year follow-up. Overall, 64% of patients were alive and without interim cardiovascular events or need for revascularization at a mean follow-up of 5 years. Most patients (79%) demonstrated improved early stress perfusion scintigraphy. The frequency of death and major adverse cardiovascular events was significantly lower in this group of patients than in the remaining Nonresponder group (23 vs. 86%; $p<0.01$). The low frequency of patients with post-treatment events suggests that EECP may be a long-term, cost-effective, noninvasive treatment for chronic angina pectoris in responding patients.

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