Appendix A: General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can

be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Screening and Characteristics of Screening Tests

Screening refers to the detection of previously undetected disease or conditions through history, physical examination, or testing. When deciding what diseases to include in screening programs, several factors are typically considered such as the burden caused by the disease, the availability of an appropriate screening test, the availability of effective treatments and evidence that early treatment from early detection leads to better health outcomes.

Since screening tests attempt to identify unrecognized disease in asymptomatic individuals and are typically performed in general average risk populations, certain characteristics of screening tests should be considered, such as sensitivity (the proportion of people with the disease who have a positive test for the disease), specificity (the proportion of people without the disease the disease who have a negative test), simplicity, cost or cost-effectiveness, safety, availability and acceptability. Ideally, a screening test should have high sensitivity, high specificity, low cost, high safety, and high acceptability to both individuals and clinicians. High sensitivity is desirable since more cases will be identified and in turn fewer cases will be missed. Since positive results are usually further evaluated, high specificity is also desirable so fewer false positive results will be obtained and fewer individuals will be subsequently subjected to unnecessary and potentially harmful confirmatory tests and interventions.

In addition, the positive predictive value (PPV) of a screening test is frequently discussed. PPV refers to the probability of having a particular disease if the test result for the disease is positive; and takes into account the prevalence of the disease. Generally, the PPV of a screening test is usually low even if the screening test has a high sensitivity and specificity, since prevalence of the particular disease is usually low in asymptomatic screening populations. Likewise, the negative predictive value (NPV) of a screening test refers to the probability of not having a particular disease if the test result for the disease is negative.

Similar to costs, cost effectiveness or cost effectiveness ratios are also commonly considered for screening tests. Cost effectiveness analysis takes into consideration the "net cost of implementing an intervention with the effectiveness of the intervention" (Haddix AC, Teutsch SM, Shaffer PA, Dunet DO. *Prevention Effectiveness*. Oxford University Press, New York, 1996, ISBN 0-19-510063-8). Cost effectiveness is often expressed as net cost per net effectiveness. Commonly for cancer screening, cost effectiveness analyses have reported results

as cost per life saved or cost per cancer averted. A ratio of $50,000 or less per life saved is often accepted by health economists as indicating that the intervention is “cost-effective.”

Appendix 2
CMS Review Table for External Counterpulsation

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Amsterdam E 1980. Clinical Assessment of External Pressure Circulatory Assistance in Acute Myocardial Infarction.	Multicenter Prospective Randomized Control Trial N= 258	**EPCA** **Control** N= 142 116 Males= 80.4% 86.2% White= 85.4% 89.7% Age= no significant difference between groups. No significant difference between groups for clinical cardiac history and treatment with regard to antiarrhythmic, positive inotropic, diuretic and vasodilator therapy.	I=External Pressure Circulatory Assistance with pressure up to 260 mmHg for a duration of up to 250 min. for tx. group O=Mortality, Morbidity	Treatment group mortality with 4 or more hours of treatment within the first 24 hours after admission = 6.5%. Treatment group with 3 or more hours of treatment showed a significant lessening of morbidity with recurrent chest pain, progression of cardiac failure, occurrence of ventricular fibrillation, change in heart size and clinical cardiac functional status at discharge.	Control group mortality = 14.7%
Arora RR 1999. The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes.	Multicenter RCT patient blinded, medical staff not blinded N=139 Intervention=72 Control= 67	Inclusion Criteria: 1. 21 to 81 years of age; 2. Symptoms consistent with CCSC angina level I, II, III; 3. Documented evidence of CAD; 4. Have ETT positive for ischemia. Mean age: Intervention = 66 Control = 71 Multiple exclusion criteria. Both groups predominantly white.	I=35 hrs counterpulsation over 4 to 7 weeks. Intervention at 300mm Hg Control at 70 mm Hg Outcomes= 1. Exercise duration 2. Exercise treadmill time to $\geq$1mm ST-segment depression 3. Avg. daily angina attack count 4. Nitroglycerin usage	1. Exercise duration was 426 $\pm$ 20 s at baseline (BL) and 470 $\pm$ 20 s posttreatment (post). 2. Time to $\geq$ 1mm ST-segment depression 337 $\pm$ 18 at BL and 379 $\pm$ 18 post. 3. Angina Counts at BL 0.76 $\pm$ 0.15 and 0.55 $\pm$ 0.27 post. 4. Nitroglycerin usage was 0.47 $\pm$ 0.13 at BL and 0.19 $\pm$ 0.07 post. 5. Adverse events = 54.9% 59 of 72 completed trial.	1. 432 $\pm$ 22 at BL and 464 $\pm$ 22 post. 2. 326 $\pm$ 21 at BL and 330 $\pm$ 20 post. 3. 0.76 $\pm$ 0.13 at BL and 0.77 $\pm$ 0.2 post. 4. 0.51 $\pm$ 0.15 at BL and 0.45 $\pm$ 0.19 post. 5. 25.8% 65 of 67 completed

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Arora RR 2002. Effects of Enhanced External Counterpulsation on Health-related Quality of Life Continue 12 Months After Treatment: A Substudy of the Multicenter Study of Enhanced External Counterpulsation	Cohort Sub-Study of MUST-EECP RCT. N= 71	**Inactive** **Active** N= 35 36 Age 62.7 65.3 Male % 94.3 88.9 White % 94.3 88.9 CCSC % I 28.6 38.9 II 40.0 55.6 III 31.4 5.6	I= EECP 35 hours O= HQOL at 1 year follow-up	HQOL improvement scores of the active (intervention) group were larger than those of the inactive group at 1 year. Only some comparisons were statistically significant. Study was underpowered.	NA
Bagger J 2004. Effects of Enhanced External Counterpulsation on Stress Radionuclide Coronary Perfusion and Exercise Capacity in Chronic Stable Angina Pectoris.	Case Series consecutive patients with stable angina pectoris with positive dobutamine stress echocardiogram (DSE). N=23	Mean age= 64 Men/women 22/1	I= EECP O= Effects of EECP on dobutamine stress induced wall motion score (WMS).	**Before Tx** **After Tx** **p** DSE Positive DSE % 100 57 WMS at rest 24.2 24.7 0.7 WMS at peak stress 30.0 28.6 0.2 Chest pain 17 17 NS	NA
Fitzgerald C 2003. Enhanced External Counterpulsation as Initial Revascularization Treatment for Angina Refractory to Medical Therapy.	Retrospective Comparative Cohort Study from IEECP registry. Group 1 - Prior percutaneous coronary intervention (PCI) and/or CABG N=4,239 Group 2 – (PUMPERS) candidates for PCI and /or CABG and had EECP as initial tx. N= 215.	Mean Age: Non-PUMPER = 66.4 PUMPER = 67.1 Male: Non-PUMPER = 75.4%, PUMPER = 72.9%. White Race: Non-PUMPER = 94%, PUMPER = 86.4%. Angina class III and IV: Non-PUMPER = 83.9, PUMPER 57.2.	I= ECP mean 34 h O = At 6 month follow-up 1. angina class III and VI, 2. angina episodes/week, 3. Nitroglycerin use 4. MACE	**Non-PUMPERS** **PUMPERS** 1. Class III & IV 24.3 8.1 2. angina episodes 4.7 1.9 3. Nirtoglycerin Use 45.3 19.5 4. Death/MI/CABG/PCI 10.6 8.0 Mortality was similar in both groups.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Holubkov R 2002. Comparison of Patients Undergoing Enhanced External Counterpulsation and Percutaneous Coronary Intervention for Stable Angina Pectoris.	Comparative Study of 2 Cohorts. EECP pts. from IEPR. PCI pts. from NHLBI Dynamic Registry.	**Group** **IEPR** **PCI** N= 323 448 Age= 65.7 64.5 Age > 65 % 54.8 48.7 Male % 79.9 72.3 Prior PCI % 53.0 33.3 Prior CABG % 42.1 18.6 Prior MI % 56.4 27.8 CHF % 16.8 9.2	I= EECP or PCI O= Mortality including death from all causes.	**Group** **IEPR** **PCI** Completed tx. % 85.8 92.1 Survival @ 1 year % 98.7 96.8 One year symptoms according to angina status significantly higher among IEPR patients. PCI superior to EECP in terms of eradicating anginal symptoms at 1 year. Baseline angina status was not equivalent in the 2 cohorts.	NA
Kern M 1985. Effects of pulsed external augmentation of diastolic pressure on coronary and systemic hemodynamics in patients with coronary artery disease.	Prospective Study Patients selected from patients with exert ional or atypical angina pectoris scheduled for cardiac catheterization for routine clinical indications. N = 14 Male = 14	Avg. age = 52 Avg. EF = 64 Men with coronary artery disease and normal left ventricular function.	I = ECP O = Effects of ECP on coronary and systemic hemodynamics: coronary blood flow data, systemic hemodynamics and transmyocardial oxygen contents obtained (1) at rest, (2) at rest following application of the ECP device but not active, (3) after 10 to 15 minutes of leg compression, and (4) 5 minutes after termination of tx.	Reduction in peak systolic pressure occurred in 8 of 14 patients. Increased mean arterial pressure and the diastolic pressure-time index, with no change in the systolic pressure-time index, absolute coronary sinus, or great cardiac vein blood flow.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Lakshmi MV 2002. Relation of the Pattern of Diastolic Augmentation During a Course of Enhanced External Counterpulsation (EECP) to Clinical Benefit (from the International EECP Patient Registry [IEPR]).	Analysis of IEPR patients who completed 35 hrs. tx. with recorded values for DA peak ratio at first and last hours. N = 2,486	Pattern of DA above or below the median value at the first and last day of EECP. **1st - Last** Low-Low = LL Low-High= LH High-Low= HL High-High= HH **LL LH HL HH** Age 68.2 66.2 66.7 64.5 Male % 70.8 73.7 75.6 86.0	I= EECP O= Relationship of DA to clinical benefit.	**LL LH HL HH** **Variable N=** Post EECP 1009 281 250 946 @ 6 months 757 217 206 756 **Decrease in mean angina class** Baseline to 35h 1.54 1.72 1.38 1.44 @ 6 months 1.59 1.67 1.47 1.53 **Patients with decrease in ≥ 2 angina classes** Baseline to 35 h % 44.6 49.3 37.3 44.0 @ 6 months % 46.1 53.9 38.9 45.9	NA
Lawson W 2000. Long-Term Prognosis of Patients with Angina Treated with Enhanced External Counterpulsation: Five-Year Follow-Up Study.	Case Series of consecutive patients. N= 33 Responders (R) = 26 Nonresponders (NR) = 7	Mean age = 61.4 years Men = 31	I=EECP O= Effect of EECP on long term prognosis.	21 of 33 patients remained alive and without MACE and the need for revascularization with 5 year follow-up. 4 deaths and 8 pts. with cardiovascular events.	NA
Lawson W 2000. Treatment Benefit in the Enhanced External Counterpulsation Consortium.	Case Series Study N= 2,289 consecutive patients enrolled in the EECP Consortium.	Avg. Age = 65.8 years Male = 79.7% White = 92.4% All patients had angina classes I thru IV.	I = EECP O= Anginal class	Completed 35 hrs tx = 60.2% > 35 hrs. tx = 18.2% Improved anginal class = 73.4% The mean change in anginal class was dependent on pretreatment class. Improvement was greater for class III and IV.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Lawson W 2001. Benefit and Safety of Enhanced External Counterpulsation in Treating Coronary Artery Disease Patients with a History of Congestive Heart Failure.	Retrospective Cohort Study from IEECP Registry. Comparison of patients with heart failure to patients without heart failure. N = 548 with a history of heart failure. N= 1409 without history of CHF	CHF cohort: Mean age = 67.1 ± 10.9 Males = 72.4% Avg. duration of CAD = 12 years, 80% with prior MI, 86% prior revascularization, 64% PCI, 71% previous CABG. Numerous other physical findings. Non-CHF cohort: Mean age = 66.0 ± 10.5 Males = 78% Avg. duration of CAD, prior MI, prior revascularization attempts were all lower than the CHF cohort.	I= CHF cohort received mean EECP tx. = 33.1 h. Non-CHF cohort received EECP tx. = 34.7. O= Angina class improvement, MACE, QOL benefit	In comparing the outcomes of the 2 cohorts,: Fewer CHF patients completed the course of treatment. At 6 months: **CHF** **Non-CHF** MACE 14.4% 8.6% Death 7.9% 2.2% CABG 1.1% 2.0% PCI 2.5% 2.9% MI 3.6% 2.5% CHF 7.2% 2.4% Cardiac Hosp. 19.1% 13.6% Unstable angina 9.0% 7.4% 82% of pts. in CHF cohort without MACE reported angina was the same or less. Mean improvement in CCS angina class was less in the CHF group vs non-CHF group.	NA
Lawson W 2004. Effectiveness of Enhanced External Counterpulsation in Patients with Left Main Disease and Angina.	Cohort Study for left main coronary artery disease (LMD) from IEECP. N=2861	Cohort divided into 3 groups. Significant LMD ≥ 70% stenosis. 1. No LMD N= 2,377 2. LMD no CABG N=53 3. LMD with CABG N=431 **Gp.** **1** **2** **3** Age 65.7 71.4 67.3 Male 73.5% 77.4% 83.5% White 93.1% 96.2% 96.0% CHF 28.2% 41.5% 39.8% LVEF 47.2% 46.3% 43.0%	I= EECP O= Improvement in CCS classification, weekly anginal episodes, frequency of nitroglycerin, adverse events.	The CCS classification improved comparably in all groups. **Group** **1** **2** **3** Angina episodes/week 7.1 7.6 8.0 Nitroglycerin / week 6.6 8.9 8.1 DC nitroglycerin 84.7% 80.6% 83.2% MACE 1.7 7.6 2.5 Late mortality in pts. with LMD no CABG was 13.2% vs 4.8% in those with LMD with CABG and 2.8% in pts. without LMD.	NA
Lawson W 2005. Angina Patients With Diastolic Versus Systolic Heart Failure Demonstrate Comparable Immediate and One-Year Benefit From Enhanced External Counterpulsation.	Cohort Study from IEECP Registry. N= 746 Pts. not defined by NYHA as to severity of CHF at baseline.	**LVEF** **<35%** **>35%** N= 355 391 Age 67.1 66.9 Male % 79.1 65.8 CCSC III/IV 90.9% 92.0%	I= EECP O= MACE, CCSC.	**LVEF** **<35%** **>35%** CCSC reduced by ≥ 1 72.2% 71.9% MACE 3.1% 2.3% MACE 15 months from 1st tx 23.8% 24.4% More rigorous evaluation of the impact of EECP on clinical outcomes will require a randomized trial.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Lawson L 2005. Predictors of Benefit in Angina Patients One Year after Completing Enhanced External Counterpulsation: Initial Responders to Treatment versus Nonresponders	Case Series of consecutive patients from International EECP Patient Registry. N= 2,007	Age = 66.4 Male % = 75.4 White% = 95.1 Prior CAD = 11 years Prior MI % = 70.4 History of CHF % = 31.9 Unstable angina % = 2.6	I= EECP O= MACE rates for initial nonresponders and responders at 1 year.	NR = nonresponders R= responders **At one year %** **NR** **R** Death 6.0 5.0 MI 5.6 5.3 CABG 4.3 2.8 PCI 11.2 5.8 CABG or PCI 14.6 8.2 MACE 22.8 16.1	NA
Linnemeier G 2003. Enhanced External Counterpulsation in Management of Angina in the Elderly.	Prospective Observational Study of patients from International EECP Registry $\geq$ 80 years old. N= 249	80 years old or older. Mean age = 84.4 $\pm$ 4 years. Female = 30%.	I= EECP O= MACE, Cardiac hospitalization, reduction in angina class, weekly angina episodes and nitroglycerin use.	Death=6 MI = 3.8 PCI = 1.1 CABG = 1.1 Cardiac hospitalization = 6 When compared to younger group mortality rate (not age adjusted) was slightly higher. Angina class decreased by $\geq$ 1 in 76%. Weekly angina episodes and nitroglycerin use decrease by 6 episodes.	Comparative group < 80 years old. Death = 3 MI = 2.7 PCI= 3.1 CABG = 1.3 Cardiac Hosp. = 12 CCSC decrease = 82%. Decrease in angina episodes and nitro usage = 7.
Michaels A 2001. Does Higher Diastolic Augmentation Predict Clinical Benefit from Enhanced External Counterpulsation?: Data from the International EECP Patient Registry (IEPR).	Prospective Study N = 1,004 Inclusion criteria – only pts. who completed the full course of at least 35 h of tx. and had 6-month follow-up were included.	Age 65 or older = 577 Age less than 65 = 427 Male = 770 Female = 231 HTN = 690, Hyperlipidemia = 755, DM = 398, Family history = 745, Smoker = 59, non-cardiac vascular dx. = 293	I = 35 h EECP O= DA ratios and relationship to clinical benefit	6 month clinical outcomes **DA** **$\geq$ 1.5** **<1.5** Death 2.2 3.3 Unstable angina 5.1 8.7 MI 2.9 2.8 CHF 2.2 4.9 PCI 4.3 1.7 CABG 1.1 1.3 QOL good or above 50.1 38.9 Only 37% of pts. treated were able to generate a DA ratio $\geq$ 1.5.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Michaels A 2002. Left Ventricular Systolic Unloading and Augmentation of Intracoronary Pressure and Doppler Flow During Enhanced External Counterpulsation.	Prospective Cohort Study N= 10 Several exclusion criteria.	Mean Age= 55.7 Males= 7 Referred for cardiac cath for diagnostic eval: suspected coronary artery disease (n=5), severe mitral regurg before valve repair (n=3), and prior orthotopic heart transplantation for annual surveillance (n=2).	I= EECP and simultaneous left heart catheterization via right radial arterial site. O=Assessment of intracoronary, central aortic, and cardiac hemodynamics during EECP and to determine whether these acute hemodynamic effects of EECP will have a favorable profile for patients with disorders such as acute coronary syndrome or cardiogenic shock.	Increase in diastolic (93%) and mean intra-coronary pressures (16%) with a decrease in systolic pressure (-15%). Average peak velocity increased (109%). TIMI frame count showed a 28% increase in coronary flow during EECP compared with baseline.	NA
Michaels A 2004. Two-Year Outcomes After Enhanced External Counterpulsation for Stable Angina Pectoris (from the International EECP Patient Registry [IEPR].	Observational Registry Study IEPR. N= 1,097 2 year follow-up.	Age = 65.8 Male = 74.0% White = 95% Heart Failure = 32.4% LVEF = 46.2%	I= EECP O= CCSC, anginal episodes per wk., adverse events, QOL.	**Immediate** **2 years** CCSC < pre EECP 73.0% 74.9% Anginal episodes/wk 2.8 6.1 Event free survival 92.8%* 40.8%# QOL good to excellent 79% 74% *event free survival is defined as freedom from death, MI, unstable angina, heart failure exacerbation, coronary revascularization. # add cardiac hospitalization, and repeat EECP to *. 82% completed the course of therapy.	NA
Soran O 2002. Enhanced External Counterpulsation as Treatment for Chronic Angina in Patients With Left Ventricular Dysfunction: A Report From the International EECP Patient Registry (IEPR).	Case Series Feasibility Study from IEPR. N=1,402: EF>35% = 1090 EF≤35% = 312	**EF= >35% ≤ 35%** Age 66.0 66.9 Male 75.5% 80.4% CHF 20.1% 60.6% Unstable angina 1.7% 4.8%	I= EECP O= Adverse events, improvement in angina.	**AT 6 months post tx.** **EF= >35% ≤ 35%** 6 months follow-up 85.7% 80.1% Death/MI/PCI/CABG 8.3 15.4 Exacerbation CHF 3.7 9.9 Angina =or < post 83.8% 81.0% Unstable angina 7.5 8.0 Angina class I/II or none 83.3 72.7 Patients with LV dysfunction suffered more adverse events.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Soran O 2002. Enhanced External Counterpulsation in Patients With Heart Failure: A Multicenter Feasibility Study.	Open, Prospective, Nonrandomized Feasibility Study. N= 32 (6 withdrew) with stable heart failure (NYHA classes II-III). Multiple exclusion criteria.	Age= 56.3 years Females= 18.8% LVEF= 23.2 Ischemic etiology of HF = 21 Idiopathic cardiomyopathy= 11	I= EECP O= Peak oxygen uptake, exercise duration, QOL, adverse events.	6 of 32 patients withdrew prior to tx., 3 pts. were discontinued during tx., 23 completed tx. Total of 19 pts. were evaluated at 6 months. Peak oxygen uptake for 23 pts. at 1 week post tx. increased from 14.99 to 15.98mL/kg/min. At 6 months, for 19 pts., peak oxygen uptake increased from 14.78 to 18.41mL/kg/min. Exercise duration at 1 week increased from 627.63 sec at baseline to 732.96 sec. At 6 months exercise duration increased from 637.13 sec. to 715.17 sec. 24 pts. had a MLHFQ test and at 1 week post-treatment overall changes were significant. At 6 months for 22 patients total score showed persistent improvement over baseline. 46 adverse events in 23 patients.	NA
Soroff H 1974. External Counterpulsation, Management of Cardiogenic Shock After Myocardial Infarction.	Prospective Cohort Study N= 20	Patients in cardiogenic shock following MI. Age range= 47 to 78 years old Males= 15	I= ECP from 33 to 480 minutes. There were multiple other interventions to treat patients condition. O= Survival	11 pts. died during or soon after tx. 1 pt. survived for 3 days. 1 pt. survived for 3 weeks 7 pts. were discharged.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Springer S 2001. Psychosocial Effects of Enhanced External Counterpulsation in the Angina Patient: A Second Study.	Prospective Study with consecutive enrollment of all patients with a dx of angina refractory to medical or surgical intervention. Follow-up study to test for psychological effects. Multiple exclusion criteria. N = 28	Male = 28 All had CAD.	I = 35 hours of EECP. O = pre- and post tx stress radionuclide scan and exercise tolerance test, and Subjective Pain and Disability Assessment (SPDA) and 4 psychological test pre- and post tx., other measures Answer the following questions: 1. Are results consistent with earlier finding for significant improvement in refractory angina? 2. Is EECP associated with alteration in depression, anxiety, hostility, anger, somatization and general psychological distress? 3. Are psychosocial alterations consistent between subset of patients? 4. Is EECP well tolerated psychologically and socially as indicated in QOL measures? 5. Do any pretest psychosocial variables have significant association with patient response to EECP with physiologic improvement of ischemia?	27 of the 28 patients enrolled submitted SPDA and QOL questionnaires. 26 completed the GHQ, 22 completed STAI, 25 completed the BDI, and 21 completed the SCL. 1. Pts. angina frequency, severity and use of antianginal medication all decreased significantly regardless of thallium result. 2. EECP therapy is associated with reduction in levels of general psychological distress, depression, anxiety, and somatiztion. 3. Amelioration in general measures of distress tended to parallel physiologic improvement in ischemia, with only one measure, SCL-90-R General Symptom Index, showing significant amelioration for those with unchanged ischemia. 4. In 11 out of 12 QOL indicators only 1 out of 27 patients reported a worsening of QOL. 89% of patients reported some improvement. 5. No pre-treatment psychosocial variable had a statistically significant association with the posttreatment outcome of improved or unchanged perfusion.	NA
Stys T 2001. Acute Hemodynamic Effects and Angina Improvement with Enhanced External Counterpulsation.	Case Series from EECP Clinical Consortium N= 395 Multiple exclusion criteria.	Age = 66.1 Male = 316 Female = 79	I= EECP O= Relationship of effectiveness ratio (ER)to posttreatment improvement in CCS angina class.	There are differences in ER between men and women and between patients aged $\leq$ 66 and > 66. No clinical relevance of ER to posttreatment improvement.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Stys T 2002. Effects of Enhanced External Counterpulsation on Stress Radionuclide Coronary Perfusion and Exercise Capacity in Chronic Stable Angina Pectoris.	Case Series over 7 years N = 175	Mean age = 61 ± 9.5 years. Male = 88%.	I = ECP 225 – 275 mm Hg O= Improvement in angina class, improvement in RPST perfusion images.	85% reported improvement in angina of ≥ 1 CCS angina class. 83% of patients in centers performing the same level of exercise pre- ad post-ECP had significant improvement in RPST perfusion defects. Exercise time was 7.46 ± 2.85 pre- vs 7.62 ± 3.01 post tx., and double product of 20,816 ± 5,411 pre- vs 19,786 ± 4,939 post tx. Maximal RPST patients revealed improvement in exercise duration 6.61 ± 1.88 pre- vs 7.41 ± 2.03 min. post tx. No significant change in double product. 54% showed improvement in RPST defects.	NA
Taguchi I 2000. Comparison of Hemodynamic Effects of Enhanced External Counterpulsation and Intra-Aortic Balloon Pumping in Patients With Acute Myocardial Infarction.	Cohort Study N=39 Compared EECP with Intra-aortic balloon pump (IABP).	**Variable** **EECP** **IABP** Age 61 62 Male % 91.3 75.0 LVEF 51.5 57.4	I= IABP or EECP O=Measure hemodynamic effects of EECP compared with IABP	EECP effects on the systemic arterial system are similar to those of IABP. Increases in cardiac preload, shown by increases in right atrial and pulmonary capillary wedge pressure, caused an increase in cardiac index in the EECP group. Limitation of study is that the hemodynamic state of the subjects was stable.	NA
Tartaglia J 2003. Exercise Capability and Myocardial Perfusion in Chronic Angina Patients Treated with Enhanced External Counterpulsation.	Prospective Study Compared pre and post tx maximal exercise radionuclide testing. N= 25	Mean age = 68 ± 9 years. Male = 92% White = 88% Angiographically proven CAD. With > 70% stenosis in 1 or more major coronary arteries or having undergone CABG.	I = 35 hours EECP O = Exercise capacity and myocardial perfusion.	84% had reduction in at least 1 anginal class. Total treadmill time: increase from 357 ± 93 pre to 449 ± 97 post. Peak double product increased from 18,891 to 20,464 ($p < 0.03$) 64% had improved nuclear scores on stress study. Of 16 with ST-segment depression on pre tx, 3 had no ST-segment depression and 10 had significant delay in their time to ST-segment depression. Stress tests were not blinded and it was not possible to eliminate an exercise training effect.	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results Intervention Group	Control Group
Urano H 2001. Enhanced External Counterpulsation Improves Exercise Tolerance, Reduces Exercise-Induced Myocardial Ischemia and Improves Left Ventricular Diastolic Filling in Patients With Coronary Artery Disease.	Prospective 2 phase inpatient study: first phase was control phase with patients sedentary or mild exertion; second phase was the EECP tx period. N = 12 Multiple exclusion criteria (same as MUST-EECP).	Age = 51 to 78 years old Males = 9 8 had effort angina 4 had silent myocardial ischemia	I = 35 sessions of ECP while hospitalized with before and after exercise thallium -201 scintigraphy, gated blood pool cardiac scintigraphy and cardiac catheterization. O = 1. Exercise test results, 2. Myocardial perfusion abnormalities, 3. hemodynamics and collateral vessels, 4.gated blood pool cardiac scintigraphy, 5. humoral factors.	After tx results: 1.Exercise duration 416 ± 101 Exercise tolerance METs 7.1 ± 1.2 Time to 1-mm ST seg. dep. 320 ± 95 s RPP at peak exercise 22,400 ± 3,700 RPP at 1-mm ST seg. dep. 18,500 ± 2,600 2. Normal perfusion imaging 67% Abnormal perfusion imaging 33% Fixed perfusion defects 13% Reversible perfusion defects 21% 3. Hemodynamics and collateral vessels: Left ventricular end-diastolic pressure 9 ± 4 Other parameters did not change. Rentrop score did not change. 4. Heart rate and systolic ejection did not change after tx., however in the parameters of diastolic filling PFR significantly increased and time to PFR decreased. 5. Plasma levels of ANP did not change, but plasma level of BNP decreased.	Before tx results: 1. 334 ± 90 5.9 ± 1.2 266 ± 106 s 21,100 ± 3,500 16,000 ± 2,3000 2. 50% 50% 15% 54% 3. 12 ± 3
Vijayaraghavan K 2005. New Graduated Pressure Regimen for External Counterpulsation Reduces Mortality and Improves Outcomes in Congestive Heart Failure: A Report From the Cardiomedics External Counterpulsation Patient Registry.	Retrospective Analysis Report from Cardiomedics ECP Patient Registry N= 127	**D/S Ratio Gp. Low Mid High** N= 54 39 34 Avg. Age 68.2 69.7 69.7 Male % 79.6 79.5 82.4 NYHA II % 11.1 22.5 36.1 III % 77.87 60.0 41.6 IV % 11.1 15.0 16.6	I= Graduated pressure ECP O= Mortality, LVEF, NYHA CHF class, incidence of all-cause hospitalizations.	**Period 1 year following tx.** **D/S Ratio Gp. Low Mid High** Mortality % 1.85 7.69 8.82 LVEF improved* % 23.0 20.1 17.5 NYHA class improved*% 36.6 29.6 29.6 Hospitalization reduced % 87.5 83.2 46.2 *survivors	NA

Author, Year and Title	Study Design	Demographics	Interventions (I) and Outcome Measures (O)	Results	Control Group
				Intervention Group	
Weisfogel G 2001. External Counterpulsation Produces a Significant Reduction in Stable Angina Class, Episodes, Medication Use, and Hospitalization.	Multicenter Retrospective Study assessment of data. N=58	Mean age = 70 $\pm$ 10 years. Male = 72% CCSC: II = 27 III = 23 IV = 8 Several other inclusion criteria.	I = 30 to 35 treatments with CardiAssist TM ECP system. O = Changes in CCS functional class, angina incidence, hospitalization incidence, nitroglycerin usage.	CCs functional class: 84% had reduction and 16% showed no improvement. Angina incidence: 91% had reduction. Hospitalization incidence: 96% reduced hospitalization rate in 6 months following compared to 6 months before. Nitroglycerin usage: 77.4% decrease in consumption of nitroglycerin	NA

Appendix C

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