EECP® Newsletter

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A Comparison Of Enhanced External Counterpulsation (EECP®) Therapy with Ranolazine (Ranexa®) for the Treatment of Refractory Angina

By John CK Hui, Ph. D.

Currently antianginal medications including beta-blockers, calcium-channel blockers, long lasting nitrates and revascularization by percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG) are the usual treatments for the more than 10 million patients suffering from chronic angina pectoris. In spite of these arrays of treatment, about a quarter to a third of these patients still continue to suffer with persistent symptoms, known as refractory angina. The U.S. FDA has cleared a noninvasive medical device Enhanced External Counterpulsation (EECP®) and a medication Ranolazine (Ranexa®) for the treatment of these chronic angina patients. This document compares the characteristics, mechanisms of actions, safety, clinical and cost effectiveness of these two treatment methods.

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Vasomedical Receives FDA 510(k) Clearance on Four New Ambulatory Monitoring Devices

Model 1303

Model 1304

Model 1305

Model 1805

Model 2301

Model 2302

Reliable and comprehensive patient information is crucial to early diagnosis and therefore successful treatment of cardiovascular diseases, which continue to increase in occurrences in the population worldwide. The collection and analysis of multi-parameter data, with full disclosure provides valuable physiological information the physician needs to more accurately identify cardiac irregularities and assess the effect of a specific course of treatment.

Vasomedical is proud to announce FDA 510(k) clearance for the Vasomedical-BIOX™ 1303 Ultra Compact 3-Channel ECG Holter Recorder, 1304 12-Channel ECG Holter Recorder, 1804/1805 Ambulatory Blood Pressure Monitors and 2302 Combined 12-Channel ECG Holter and Ambulatory Blood Pressure Monitor.

These new Vasomedical-BIOX™ models, together with the already FDA cleared Model 1305 3-channel ECG Holter Recorder, Model 2301 Combined 3-Channel ECG Holter and Ambulatory Blood Pressure Monitor, and CB Series Analysis and Reporting Software form a complete line of ambulatory monitoring products for long term recording and analysis of ECG and blood pressure data, offering flexible solutions to clinicians for various diagnostic needs. All Vasomedical-BIOX™ series monitors work with the CB Series Analysis and Reporting Software.

HIGHLIGHTS

Current Issue

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A Comparison Of Enhanced External Counterpulsation (EECP®) Therapy with Ranolazine (Ranexa®) for the Treatment of Refractory Angina (Cont'd.)

	EECP®	Ranexa®
FDA cleared or approved indications	▪ stable or unstable angina pectoris ▪ congestive heart failure ▪ acute myocardial infarction ▪ cardiogenic shock_ **CMS National Coverage Policy** has extended Medicare coverage to include EECP® for angina patient not readily amenable to invasive procedure	Treatment of chronic angina, may be used with beta-blockers, nitrates, calcium channel blockers, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.
Dosage	▪ 1 to 2 hours daily, 5 times/week for one course totaling 35 hours. ▪ Benefits of one course has been reported to last up to five years ▪ Benefits achieved with repeat treatment	▪ The maximum recommended daily dose of Ranexa is 1000 mg twice daily. ▪ 7 days/week for life
Contra-indications	▪ arrhythmias that interfere with machine triggering ▪ bleeding diathesis ▪ active thrombophlebitis ▪ severe lower extremity vascular occlusive disease ▪ presence of a documented aortic aneurysm requiring surgical repair ▪ pregnancy	▪ Taking strong inhibitors of CYP3A including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir and saquinavir. ▪ Taking inducers of CYP3A including diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products. ▪ Clinically significant hepatic impairment: Plasma concentrations of ranolazine were increased by 30% in patients with mild (Child-Pugh Class A) and by 60% in patients with moderate (Child-Pugh Class B) hepatic impairment.
Warnings and Precautions	▪ Decompensated heart failure (i.e. central venous pressure > 7 mm Hg, and pulmonary edema) ▪ Severe pulmonary hypertension (pulmonary artery > 50 mm Hg) ▪ Uncontrolled systemic hypertension (> 180/110 mm Hg) ▪ Severe aortic insufficiency ▪ Warfarin therapy with INR>3.0	▪ Ranolazine blocks calcium current (IKr) and prolongs the QTc interval in a dose-related manner, common in patients 75 years or older and patients with renal impairment ▪ Patients with family history of QTc prolongation, congenital long QT syndrome, or if they are receiving drugs that prolong the QTc interval such as: Class Ia (e.g., quinidine) or Class III (e.g., dofetilide, sotalol, amiodarone) antiarrhythmic agents, erythromycin, and certain antipsychotics (e.g., thioridazine, ziprasidone)
Mechanism of Action	▪ Hemodynamic Effects o Diastolic augmentation: increases coronary blood flow o Venous return: increases stroke volume and cardiac output o Systolic unloading: reduces myocardial workload ▪ Angiogenesis effects o Develop collateral circulation o Increases coronary flow reserve o Release vascular growth factors o Increases microcirculation density ▪ Improves Endothelial Function o Increases circulating endothelial progenitor cells o Increases nitric oxide level o Improves flow mediated dilation o Reduces smooth muscle cells proliferation and migration ▪ Reduces anti-inflammatory / adhesive molecules ▪ Reduces arterial stiffness	▪ Hemodynamic Effects o Minimal changes in mean heart rate (< 2 bpm) and systolic blood pressure (< 3 mm Hg). ▪ Antianginal Effects o Inhibit the cardiac late sodium current (INa). However, the relationship of this inhibition to angina symptoms is uncertain. o The QT prolongation effect of Ranolazine on the surface electrocardiogram is the result of inhibition of IKr, which prolongs the ventricular action potential ▪ Metabolic pathway o Shifting from free fatty acid oxidation to carbohydrate oxidation, produces more efficient use of oxygen
Clinical Effectiveness Chronic Angina	▪ Δ in total exercise time (Bruce protocol*) versus placebo o 6 sec (MUST-EECP†) o 48 sec (ESREC†) o 187 sec (Braith) P<0.001 vs. sham Naughton Protocol ▪ Δ in time to 1 mm ST-segment depression o 49 sec (MUST-EECP†) ▪ Δ in time to angina o 239 sec (Braith) P=0.003 vs. sham Naughton Protocol ▪ Δ CCS angina classification o 85% improved ≥ 1 CCS Class post EECP (ESREC†) o 83% improved ≥ 1 CCS Class post EECP(IEPR Design†) o 74.9% improved ≥ 1 class at 2-year (IEPR†) o 77.9% improved ≥ 1 class at 3-year (IEPR†) ▪ Δ Angina Episodes/week (AF) o 0.24 versus control (MUST-EECP†) o 10.1±12.9 at baseline to 2.5±5.8 post EECP (IEPR (IEPR†) o 6.1±10.4 at 2-year follow-up (IEPR†) o 6.0 at 3-year post-EECP (IEPR†) o 12.6 pre versus 3.5 post, P<0.01 vs. sham (Braith) ▪ Δ Nitroglycerin Usage/week (NU) o 0.22/week relative to placebo (MUST-EECP†) o 61.7% discontinued usage baseline (IEPR Design, Baseline†) o 9.5±11.9 at baseline to 2.7±6.5 post-EECP (IEPR (IEPR†) o 8.1±13.0 at 2-year follow-up (IEPR†) o 3.0 at 3-year post-EECP (IEPR†) o 7.7 pre versus 1.4 post, P<0.01 vs. sham (Braith) ▪ Quality of Life (QoL) o 66% improved QoL (IEPR Design, Baseline†) o 55% improved at 2-year (IEPR†) o Improvement sustained at 3-year follow-up (IEPR†)	▪ Δ in total exercise time (modified Bruce protocol*) versus placebo o 50.1±7.2 sec (MARISA**) o 23.7±10.9 sec (CARISA**) ▪ Δ in time to angina o 56.4.1±8.5 sec (MARISA**) o 29.7±12.1 sec (CARISA**) ▪ Δ in time to 1 mm ST-segment depression o 55.6±8.2 sec (MARISA**) o 19.9±12.2 sec (CARISA**) ▪ Δ Angina Episodes/week (AF) o Baseline 4.5, to 3.3±0.3 in placebo and 2.1±0.2 in1000 mg (CARISA**) o 0.43 /week relative to placebo (ERICA**) ▪ Δ Nitroglycerin Usage/week (NU) o Baseline 4.2, to 3.1 in placebo and 1.8 in1000 mg (CARISA**) o 0.65/week relative to placebo (ERICA**) ▪ Quality of Life o Reduces AF and NU only when angina frequency at baseline ≥ 4/5 /week (ERICA**)
Clinical Effectiveness ACS/HF	In heart failure patients, EECP improved exercise tolerance (31.9 sec relative to control group), quality of life and NYHA functional class (33% vs 11% in control) EECP also reduced hospitalizations and emergency room visits in patient with angina and LVD	In acute coronary syndrome, Ranolazine was not effective in reducing major cardiovascular events (MERLIN-TIMI36)

* Bruce Protocol Stress test is approximately twice the workload as modified Bruce with similar duration. Stages 1 and 2 of the Modified Bruce are at a Functional Class 3 workload (2.9 and 3.7 METS) and the third Stage corresponds to the first Stage of the Bruce protocol. Thus, the person who does 9 minutes in the Modified protocol does the same workload as 3 minutes on the Bruce; 12 minutes on the Modified is the same as 6 minutes on the Bruce.

† Results of clinical studies on Enhanced External Counterpulsation:

The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP). J Am Coll Cardiol 1999; 33:1833-40).

Effects of Enhanced External Counterpulsation on Stress Radionuclide Perfusion and Exercise Capacity (ESREC). Am J Cardiol 2002;89:822-824.

Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH). J Am Coll Cardiol 2006;48:1198-205.

The International EECP Patient Registry (IEPR). Design, Methods, Baseline: Clin Cardiol 2001;24:435-442. Post-EECP: Am J Cardiol 2003;92:439-443. 2-Year Outcome: Am J Cardiol 2004;93:461-464. Long Term (3-year) follow-up: Clin Cardiol 2008;31:159-164.

Enhanced External Counterpulsation Improves Peripheral Artery Flow-Mediated Dilation in Patients with Chronic Angina, A Randomized Sham Controlled Study, Circulation.2010;122:1612-1620.

** Results of clinical studies on Ranolazine:

Monotherapy Assessment of Ranolazine in Stable Angina (MARISA). J Am Coll Cardiol 2004;43:1375-82

Combination Assessment of Ranolazine In Stable Angina (CARISA). JAMA 2004;29:309-316.

Efficacy of Ranolazine In Chronic Angina (ERICA). J Am Coll Cardiol 2006;48:566-75.

Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN-TIMI 36). JAMA 2007;297:1775-1783.

Using the data from the table listed above, we can construct the following comparison table showing the pros and cons of EECP® versus Ranexa®.

	EECP®	Ranexa®
Nature	Medical Devie	Pharmaceutical agents (oral tablet)
Current clinical applications	Chronic angina not readily amenable to revascularization	Persistent chronic angina despite use of traditional antianginal agents
Dosage	▪ 1-course 35 hours, 1 to 2 hour(s) daily for 3-7 weeks. ▪ Published clinical studies demonstrate 75% of patients responded with initial benefit and these benefits were sustained for 3-years ▪ Treatment can be repeated with similar benefits	▪ 500 or 1000 mg tablet twice daily ▪ Taken for life everyday
Side Effects	▪ Mild skin irritation	▪ Contraindicated for patients with liver and renal impairment (comorbidities in a large percentage of cardiac patients) ▪ Interact with CYP3A Inhibitors, Inducers ▪ Nursing mothers ▪ Adverse Reaction in 6% of patients with dizziness, nausea, asthenia, constipation, and headache ▪ Additional adverse interactions in 0.5 to 2% of patients with bradycardia, palpitations, vertigo, tinnitus, abdominal pain, vomiting, peripheral edema, dyspnea, hypotension and orthostatic hypotension
Mechanism of Action	▪ Hemodynamic effects during EECP ▪ Recruits collateral circulation ▪ Enhances microcirculation / angiogenesis ▪ Improves endothelial dysfunction ▪ Reduces arterial stiffness ▪ Inhibits inflammatory and adhesion cytokines ▪ Prohibits atherosclerotic process	▪ No change in heart rate and blood pressure ▪ Selective inhibition of late sodium current (INa), reduce ischemia-induced sodium and calcium overload ▪ Relationship between late INa blockade and improvement in angina is not well understood
Clinical Effectiveness Chronic Angina	▪ 49 sec increase in exercise time to ST 1-mm depression using Bruce Protocol StressTest ▪ 3-year follow-up with benefits of treatment sustained in 75-80% patients	▪ 55 sec increase in exercise time to ST 1-mm depression using Modified Bruce Protocol Stress Test at most half of the workload increase achieved by EECP ▪ No long term follow-up data
Clinical Effectiveness ACS/HF	▪ PEECH demonstrated EECP® was effective as a treatment for heart failure	▪ MERLIN-TIMI demonstrated addition of Ranexa® to standard treatment for acute coronary syndrome was not effective in reducing major cardiovascular events

In summary, from the point of view of a patient suffering from persistent angina pectoris or angina equivalent symptoms (shortness of breath, fatigue, etc.) EECP® Therapy, despite the need to receive therapy at a treatment center instead of just taking a couple of pills every day, will have better clinical outcomes, eliminates the need to take Ranexa® and possibly other medications everyday for life, and most importantly, does not carry the concerns, all the side effects and interactions with other drugs when compared with Ranexa®. From the physician's point of view, EECP® Therapy is safe, effective, has minimal side effects and can be administrated safely in the physician's office/clinic with CMS and most third party insurance coverage.

EECP® Therapy Reimbursement Update

Getting Past CMS Billing Issues

A CMS billing issue arose recently for a new provider offering EECP® therapy in southern California. The cardiology office received denials for claims submitted electronically using the HCPCS code G0166 and ICD9 413.9, even though the local CMS carrier Palmetto stated these were the proper codes to use in their policy. The denial claims were returned with a Medical Necessity denial code 50. After contacting some of the other local EECP® providers it was discovered that in the past few years, it became necessary to document, on the claim form for each patient, the name of the supervising physician. This information must be added to the Comments section on the electronic bill or in Box 19 on the paper form. The policy further states that the name had to be on the initial claim only, not every claim.

If you have a coverage denial that is frustrating you, please contact Vasomedical directly or post it on the EECP® Forum.

Understandably, this new provider was getting rather frustrated, since it seemed they were billing properly, but had difficulty getting clarification from the local CMS carrier. Sometimes when new carriers become the CMS provider in a jurisdiction, their local coverage decision policies or billing procedures may have affected the way billing was done previously. Unfortunately, this problem may also have given some EECP® providers the mistaken perception that EECP® therapy was not covered by the carrier and patient referrals or treatment was withheld. We thank our customers in southern CA who helped in this matter and hope this information can help other new or affected providers. This issue would also affect providers in NV and HI since they are also under Palmetto, but other Medicare carriers might use G0166 and ICD 9 code 413.0 Please always consult your local Medicare carrier's policy for the correct coding.

This situation is a great example of how Vasomedical working together in support of our EECP® providers functions as a "clearing house" of information. This sharing of information between providers affords maximum support in reimbursement for EECP® Therapy services. If you have a coverage denial that is frustrating you please contact Vasomedical directly or post it on the EECP® community message board at www.EECPForum.com and let Vasomedical and the EECP® community of patients, physicians, therapists and administrators see how we can help. If you have been successful in overcoming a denial please share that information directly or on the website as it makes us all more successful in obtaining better coverage for our patients. This in turn will make EECP® Therapy accessible to more patients who might otherwise be denied necessary treatment. Thank you.

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In 1995, there was one EECP center in the United States; today there are almost 700, and close to 200 internationally! In 1995, a therapists' organization was a dream, today it is reality with more than 375 members.

Education and increasing membership continue to be the mandates. Join us! Help us help you achieve professional status & recognition. IETA welcomes you to jump onboard! Become a new member, renew your previous membership and look forward to obtaining your CET this year if you already have not done so. If you have done all these things, then you are truly in support of your IETA and the future of EECP for all those people we touch with heart disease!

If you have a story idea or would like to share the results of your experience with other clinicians, please e-mail your idea/story to:
Paul Persaud, Marketing Manager at ppersaud@vasomedical.com

Recent Publications & Presentations

Effects of Enhanced External Counterpulsation on Arterial Stiffness and Myocardial Oxygen Demand in Patients With Chronic Angina Pectoris
Casey DP, Beck DT, Nichols WW, Conti CR, Choi CY, Khuddus MA, Braith RW
Am J Cardiol 2011; 107(10): 1466-1472

A Pilot Study To Examine Relationships Among External Counterpulsation, Cardiac Output, Functional Capacity, And Quality Of Life
Shanks LC
Applied Nursing Research, online 28 December 2010

Enhanced External Counterpulsation-A Review
Sayami LA, Ullah M, Rahman MT, Rahman Z, Roy D, Majumder AAS
Cardiovascular Journal 2010;2(2):236-244

Does External Counterpulsation Augment Mean Cerebral Blood Flow in the Healthy Brain? Effects of External Counterpulsation on Middle Cerebral Artery Flow Velocity and Cerebrovascular Regulatory Response in Healthy Subjects
Jungehuelsing GJ, Liman TG, Brunecker P, Ebel A, Endres M, Buschmann I, Pagonas N, Buschmann, EE on behalf of Arteriogenesis Network and the Center for Stroke Research Berlin
Cerebrovascular Diseases 2010;30:612-617

Enhanced External Counterpulsation Improves Peripheral Artery Flow-Mediated Dilation in Patients with Chronic Angina. A Randomized Sham-Controlled Study.
Braith RW, Conti CR, Nichols WW, Choi CY, Khuddus MA, Beck DT, Casey DP
Circulation 2010; 122: 1612-1620

Effect of Enhanced External Counterpulsation on Circulating CD34+ Progenitor Cell Subsets.
Kiernan TJ, Boilson BA, Tesmer L, Harbuzariu A, Simari RD, Barsness GW.
Int J Cardiol. 2010 Sep 13. [Epub ahead of print]

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