Enhanced External Counterpulsation
EECP®

A Noninvasive Therapy

Vasomedical, Inc.
Hemodynamics of the Heart

Flow = \frac{\text{Pressure}}{\text{Resistance}}

Supply: diastolic Pressure Time
Demand: Systolic Pressure Time

Energy balance

Blood Pressure (mm Hg)

Blood flow (L/min)
EECP Operation

**Diastolic Inflation**
Sequentially inflate three sets of cuffs at the end of systole

**Effects:**
- Diastolic Augmentation
- Increase Venous Return
- Increase Coronary Perfusion
- Increase Cardiac Output

**Systolic Deflation**
Simultaneously deflate all three sets of cuffs at the end of diastole

**Effects:**
- Systolic Unloading
- Reduce Cardiac Workload
- Increase Cardiac Output
Arterial Counterpulsator

Birtwell, Clauss - 1961
Early (hydraulic) external counterpulsation machine
Historical Highlights of External Counterpulsation

- **Tension Time Index** described by Sarnoff, Braunwald
- **Birtwell’s Arterial Counterpulsator** first described
- **Intra-aortic balloon pump (IABP)** Clauss, Harken 1962
- **Clinical testing of hydraulic external system on AMI and cardiogenic shock**
- Zheng designed sequential pneumatic pulsation system
- Zheng first publication on clinical use of ECP
- Birtwell, Hui design pneumatic system in US
- Lawson, Soroff and Hui at Stony Brook started EECP angina study using devices from China
- EECP introduced to US
- International EECP Patient Registry first 5,000 pts
  - Completed June 2001

**Timeline**

- 19 AP pts Banas
- 258 MI pts Amsterdam
- 18 Pts treated with EECP Lawson
- MUST-EECP completed
- Pilot CHF Study completed
- PEECH completed
Enhanced External Counterpulsation (EECP)

- EECP is a noninvasive therapy for patients with coronary artery disease.
- It applies sequential external pressure to the lower extremities at the end of systole to increase diastolic coronary perfusion pressure and venous return.
- Releases all pressure at the end of diastole to reduce peripheral vascular resistance, cardiac workload and increase cardiac output.
- A full course of EECP is 30-35 hours, 1-2 hour(s) daily for 3-7 weeks.
EECP Mechanisms of Action

Hemodynamic Effects of EECP

Increase Cardiac Output

- Improve Diastolic Filling
- Increase Venous Return

Systolic Unloading

- Increase Shear Stress on Endothelium
- Improve Endothelial Function

Increase Coronary Perfusion

- Diastolic Augmentation
- Diastolic Retrograde Flow

- Pressure Gradients

Enhance Collateral Capillary Sprouting

- Angiogenesis and Arteriogenesis

Neurohormonal Release

Increases: NO
Decreases: BNP, ANP, ET-1, ACE, ANG II

Vasodilatation

Release of Growth Factors
Hemodynamic Effects of EECP

Systolic Unloading & Diastolic Augmentation

Increase Cardiac Output
Duplex echocardiography  Descending Aorta

Lawson, Hui: J of Critical Illness 2000;5:629-636
Hemodynamic Effects

Increase Coronary Artery Blood Flow

Transesophageal Echocardiography of the left main

Doppler Flow Velocities obtained with FloWire in the LAD

Werner: XXth Congress of the European Society of Cardiology, 1998

EECP Mechanisms of Action

**Hemodynamic Effects**
- Systolic Unloading (cardiac workload↓)
- Diastolic Augmentation (coronary blood flow↑)
- Increase Cardiac Output (organ perfusion↑)

**Improve Endothelial Function**
- Vasodilation ↑
- Intimal Hyperplasia ↓

**Collateral Development**
- Blood flow to ischemic region↑
- Capillary density ↑

**Improve Neurohormonal Factors**
- BNP ↓ and ANP ↓
- Angiotensin II ↓

**Reduce Arterial Stiffness**
- Blood pressure ↓
- Vascular resistance ↓
- Cardiac efficiency ↑
Evolution of Cardiovascular Diseases

EECP is the only medical device proven to improve endothelial cell function

Endothelial dysfunction

- **Risk Factors**
  - Hypertension
  - Atherogenic Dyslipidemia
  - Diabetes Mellitus
  - Abdominal Obesity
  - Prothrombotic state
  - Proinflammatory state
  - Genetics
  - Ethnic Predisposition
  - Aging
  - Hormonal imbalance
  - Physical inactivity
  - Smoking

- **Common Factors**
  - Arterial wall thickening
  - Vascular Stiffness
  - Atherosclerosis
  - LV- contractility ↓
  - LV- relaxation ↓
  - Endothelial Dysfunction
  - Inflammation ↑
  - Catabolism ↑
  - Atrophy ↑
  - Early fatigue ↑
  - Skeletal Muscle Dysfunction
  - Ventilatory Abnormalities
  - Neurohormonal activation
  - Renal

- **Single organ Dysfunction**
  - Heart

- **Multiple organs Dysfunction**
  - Heart failure
  - Renal Failure
  - Cerebral
  - Pulmonary

Progressive
Endothelial Cell Functions

Single layer of cells lining the lumen of all blood vessels

- Vasomotor tone (vasodilation)
- Permeable barrier
- Antithrombosis
- Anti-inflammation
- Angiogenesis: growth factors
- Antioxidant
Pathophysiology of Endothelial Dysfunction

Process of Atherogenesis

Oxidative Stress, Abnormal metabolism, Low flow state

Endothelial Dysfunction

- Reduced vaso-relaxation nitric oxide
- Reduce flow-mediated vasodilatation
- Reduced blood flow
  - Increase systolic blood pressure
  - Increase arterial stiffness
    - Vascular Adhesion Molecules
      - Inflammatory responses
        - Migrate into subendothelial space
          - Promote smooth muscle cells growth, proliferation, migration
            - Increase thrombosis/leukocyte adhesion
              - Intimal Medial thickening
                - Atherogenesis: Plaque formation
                  - Cardiovascular Disease
EECP Improves Endothelial function and Vasodilation

During EECP Blood flow↑

Shear stress↑

Nitric Oxide Activates eNOs

Endothelial cell produce NO

NO crosses intimal to Smooth Muscular Cells

Release cGMP

Effects of EECP on plasma cGMP

Smooth Muscle cell relaxation

Vasodilation

Vascular resistance ↓

Blood flow ↑
Effect on Vasomotor Tone and Response

**Reactive-Hyperemia Peripheral Arterial Tonometry**

N=18 pt

<table>
<thead>
<tr>
<th>Time</th>
<th>PAT Index</th>
<th>Pre-EECP</th>
<th>Post-EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st/hr</td>
<td>1.0</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>17th/hr</td>
<td>1.5</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>35th/hr</td>
<td>1.77 ± 0.18</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td>1.5</td>
<td>*</td>
<td>†</td>
</tr>
</tbody>
</table>

Normal PAT Index: 1.77 ± 0.18

*p<0.05; †p<0.05 vs pre EECP index on 1st, 17th and 35th hr

**Brachial Artery Flow-mediated dilation (FMD)**

Control
N=20

EECP
N=20

% FMD

Baseline
2-month after Enrollment

p<0.01

JACC 2003:41,10,1761-8

Effects on Vasomotor Function

Flow-Mediated Dilation: Brachial Artery

Sham N= 14, EECP N=28

Sham: 2%↑, EECP: 51%↑

*† p<0.01

Flow-Mediated Dilation: Femoral Artery

Sham: 3%↑, EECP: 30%↑

*† p<0.01

Change in Plasma NO

Sham: 2%↑, EECP: 36%↑

*† p<0.01

Change in Endothelin -1

Sham: 5%↑, EECP: 25%↓

*† p<0.01

Braith: Circulation 2010;122:1612-1620
N=20 patients with refractory angina

Inflammatory Cytokines and Adhesion Molecules

Tumor Necrosis Factor -α

Sham N= 14, EECP N=28

High-sensitivity C-reactive Protein

Monocyte chemoattractant Protein-1

Soluble Vascular Cell Adhesion Molecule

Braith: Circulation 2010;122:1612-1620
EECP improves Reactive Oxidation Stress

Results of a randomized sham-controlled study

Asymmetrical Dimethylarginine (ADMA) eNO s inhibitor

Superoxide dismutase (SOD)

8-isoprostane (PGF$_{2\alpha}$) Lipid peroxidation marker

Plasma Norepinephrine

Sham N= 14, EECP N=28

Braith: Circulation 2010;122:1612-1620
Association with Function

**CCS Functional Class**

- **Sham**: 2.93, 3.16
- **EECP**: 1.2

Significance: *† p<0.001

**Angina Episodes per day**

- **Sham**: 1.7, 1.6
- **EECP**: 1.8, 0.5

Significance: *† p<0.01

**Peak Exercise Duration**

- **Sham**: 597, 612
- **EECP**: 586, 774

Significance: *† p<0.001

**Daily Nitrate Usage**

- **Sham**: 1.0
- **EECP**: 0.9, 1.0

Significance: *† p<0.01

**Peak Time to angina**

- **Sham**: 449, 471
- **EECP**: 406, 645

Significance: *† p<0.01

**Peak Oxygen Consumption**

- **Sham**: 16.5
- **EECP**: 16.6, 17

Significance: *† p<0.001

Sham N= 14, EECP N=28

Braith: Circulation 2010;122:1612-1620
Effects of EECP on Pulse Wave Velocity and Arterial Stiffness

Travel Time of Reflected Wave
Decreased PWV ≈ Increased Δ t_p/2

Pulse Pressure = (P_i − P_d)

Augmentation Index = (P_s − P_i) / (P_s − P_d)

Time for pressure wave to travel from aortic root and back = Δt_p

Wasted LV pressure energy = 2.09 X Δtp * (P_s − P_i)

LV Workload = Tension Time Index = area under systolic wave

J Am Coll Cardiol 2006;48:1208-1214
Arterial Stiffness and Myocardial Oxygen Demand
Results of a randomized sham control study

Pulse-Wave Velocity
Carotid – Femoral

Aortic Augmentation Index (Alx)

Wasted Left Ventricular Energy

EECP (N=28)  Sham Control (N=14)

Am J Cardiol 2011;107(10):1466-1472
Arterial Stiffness and Myocardial Oxygen Demand

Results of a randomized sham control study

Aortic Augmentation Index (Alx)

Wasted Left Ventricular Energy

EECP (N=28)  Sham Control (N=14)

Am J Cardiol 2011;107(10):1466-1472
Morphological and Structural Changes

**Increase Capillary Density**

Control Group

EECP Group

Control Region

Infarcted Region

75 μm section

European Society of Cardiol Congress 1999

**new smooth muscle cell growth**

<table>
<thead>
<tr>
<th>µm²/mm² sample field</th>
<th>Control</th>
<th>EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6,592±2,785</td>
<td>6,497±533</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Experimental AMI dog model (VEGF)**

Area stained with anti-VEGF antibody in infarcted regions (mm²/10²)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>EECP</th>
<th>p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0036±0.0028</td>
<td>0.0353±0.0111</td>
<td></td>
</tr>
<tr>
<td>N=6 dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**new endothelial cell growth**

<table>
<thead>
<tr>
<th>µm²/mm² sample field x100</th>
<th>Control</th>
<th>EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,710±1,497</td>
<td>5,667±1,894</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control

EECP

Endothelial cells stained brown

Coronary Collateral Flow After External Counterpulsation in Man

**Coronary Collateral Flow Index**

- **Baseline**
  - Sham: 0.1
  - ECP: 0.15
- **Follow-up**
  - Sham: 0.2
  - ECP: 0.3

- **p=0.14** (Sham vs. ECP)
- **p=0.006** (Baseline vs. Follow-up)

**Coronary Collateral Conductance**

- **Baseline**
  - Sham: 0.4
  - ECP: 0.6
- **Follow-up**
  - Sham: 0.2
  - ECP: 0.4

- **p=0.45** (Sham vs. ECP)
- **p=0.072** (Baseline vs. Follow-up)

**Coronary Collateral Flow Index (CFI)**

\[ \text{CFI} = \frac{\text{CAP}_{\text{occl}} - \text{CVP}}{\text{Mean aortic Pressure} - \text{CVP}} \]

**Coronary Collateral Conductance (CCC)**

\[ \text{CCC} = \frac{\text{Myocardial blood flow}}{\text{Mean aortic Pressure} - \text{CAP}_{\text{occl}}} \]

**CAP_{occl}**: Distal coronary artery pressure during balloon occlusion (mm Hg)

**CVP**: Central venous pressure

Gloecker: Heart 2010;96:202-207
**Improvement of Collateral Flow**

**Pressure-Derived Collateral Flow Index**

- Control (N=7)
- EECP (N=16)

- Baseline
- Post treatment at 7 weeks

**Fractional Flow Reserve**

- Control (N=7)
- EECP (N=16)

**Formulas**

- \( CF_{Ip} = \frac{\text{Coronary Occlusive Pressure} - \text{Venous Pressure}}{\text{Aortic Pressure} - \text{Venous Pressure}} \)

- \( FFR = \frac{\text{Distal Coronary Pressure} - \text{Venous Pressure}}{\text{Aortic Pressure} - \text{Venous Pressure}} \)

*European J of Clin Investigation 2009;39:866-875*
Circulating Endothelial Progenitor Cells (EPC) in Patients with Angina Pectoris

**Number of CD34+/KDR+ Cells**

per $10^5$ peripheral blood mononuclear cells

- Control (N=10)
- Treated (N=15)

<table>
<thead>
<tr>
<th>Number of Cells</th>
<th>Controls</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>18</td>
<td>20</td>
</tr>
</tbody>
</table>

**EPC Colony Forming Unit**

per well

- Control (N=10)
- Treated (N=15)

<table>
<thead>
<tr>
<th>Colony Forming Unit</th>
<th>Controls</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

Assessed by flow activated cell sorter

- Yellow: Baseline
- Green: Post-treatment

Cardiology 2008;110:160-166
EECP Increases Hematopoietic Progenitor Cells correlates with Clinical Improvement

Duke Activity Status Index (DASI) correlations with circulating progenitor cells

**Control Group: N=19**
- No obstructive CAD
- 7 normal, 12 abnormal endothelial function

**EECP treated group: N=13**
- Refractory CAD
- Abnormal coronary endothelial function

* p=0.02 compared with EECP baseline
◆ p=NS compared CED with day 17, 35 and 1 month postEECP therapy

![Graphs showing correlations](image_url)

- R=0.38
  - p=0.01
- R=0.50
  - p=0.006
- R=0.47
  - p=0.01
- R=0.28
  - p=0.14

International J Cardiology Sept 2010
Decrease Circulating level of Proinflammatory Biomarkers

Plasma Tumor Necrosis Factor - α

EECP

-29%

N=12

6.9±2.7 to 4.9±2.5 pg/ml, p<0.01

Sham

-5 %

6.9±1.9 to 6.7±1.9 pg/ml, p=0.54

Monocyte Chemoattractant Protein - 1

EECP

-20%

N=9

270±82 to 264±66 pg/ml, p=0.51

Sham

-0.5%

Soluble Vascular Cell Adhesion Molecule - 1

EECP

-6 %

1.4%

847±177 to 859±160 ng/ml, p=0.31

Clinical Improvement Post EECP

Canadian Cardiovascular Society Angina Class

Baseline

3.1±0.5

Post EECP

1.2±0.4

p

<0.01

Angina Episodes

Baseline

1.6±1.4

Post EECP

0.4±0.6

p

<0.05

Nitrolycerin use/day

Baseline

0.5±0.7

Post EECP

0.1±0.2

p

<0.05

Casey, Conti: Am J Cardiol 2008;101:300-302
Improvement in Neurohormonal Factors

**ANP and BNP**

![Bar chart showing changes in Human Plasma ANP and BNP](chart1.png)

**Change in Angiogenic Factors**

![Bar chart showing changes in HGF, bFGF, VEGF](chart2.png)

**Plasma cGMP**

![Bar chart showing changes in Plasma cGMP](chart3.png)

**Plasma ANG II Activity**

![Bar chart showing changes in Plasma ANG II Activity](chart4.png)
EECP improves Fasting Plasma Glucose (FPG) and 120 minutes after Oral Glucose Tolerance tests (OGTT)

Fasting Plasma Glucose (mg/dL)

Plasma Glucose 120 minutes after OGTT (mg/dL)

EECP n=12, Control n=6

J Appl Physiol 2012; 112:868-876
EECP improves Insulin Resistance in subjects with Abnormal Glucose Tolerance

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)

Whole Body Composite Insulin Sensitivity Index (C-ISI)

EECP n=12, Control n=6

J Appl Physiol 2012; 112:868-876
Mechanisms of EECP in the management of Glycemic Control in subjects with Abnormal Glucose Tolerance

Improvement in inflammatory profile

Change from baseline in high sensitivity C-reactive protein (mg/L)

Change from baseline in tumor necrosis factor – α (pg/mL)

EECP n=12, Control n=6

Mechanisms of EECP in the management of Glycemic Control in subjects with Abnormal Glucose Tolerance

Improvement in Glucose delivery and uptake in skeletal muscle

EECP increases blood flow
Improves endothelial function
Increase plasma nitric oxide

EECP n=12, Control n=6

Plasma concentrations of 8-isoprostaglandin-F2α (pg/mL)

Increases transport

Reduces lipid peroxidation

Increases vasodilation

Increases delivery

% Change in GLUT4 Glucose Transporters

Capillary Density (# of capillaries/mm²)
EECP in Primary Prevention
Effect of EECP on eNOS Protein Expression

A - C: Immunohistochemistry of eNOS localized in endothelial cells (brown)

D: Bar chart showing fluorescence intensity of eNOS as % of control in the three groups

E: Peak diastolic arterial wall shear stress (τ) in the Brachial arteries is calculated using

\[ \tau = 4 \eta V / ID \]

Atherosclerosis

Sudan IV-stained porcine aortas

High-cholesterol diet induced remarkable atherosclerotic lesions in aortas of the CHOL group. Hypercholesterolemic animals receiving EECP showed ameliorated lesions in aortas.

Percentage of plaque area: *p < 0.05 for CHOL vs Control
†p < 0.05 for CHOL+EECP vs CHOL
Effects of EECP on Intimal Hyperplasia

Left Anterior Descending Coronary Artery

CHOL group fed with high cholesterol atherogenic diet for 15 weeks
EECP started at 7½ wks, treated for 7 ½ wks

Intimal Area = (Internal elastic laminal – lumen area)
Media Area = (External elastic laminal – internal elastic laminal)

There was no significant difference between Control and CHOL+EECP
* $p<0.05$ for CHOL vs Control
† $p <0.05$ for CHOL+EECP vs CHOL

Circulation 2007;116:526-534
TUNEL Assay

Left Anterior Descending Coronary Artery

magnification ×40

magnification ×400

Control
CHOL
CHOL + EECP

High-cholesterol diet induced excessive cellular apoptosis in the CHOL group. Hypercholesterolemic animals receiving EECP showed ameliorated apoptosis in LADs.

TUNEL positive index: * $p<0.025$ for CHOL vs Control  
† $p<0.017$ for CHOL + EECP vs CHOL
High-cholesterol diet induced excessive cellular apoptosis in the CHOL group. Hypercholesterolemic animals receiving EECP showed ameliorated apoptosis in LADs.
Confocal laser scanning fluorescence microscopy of LADs

**NF-KB**

Magnification × 400

**Phospho-NF-KBp65**

**Total-NF-KBp65**

**actin**

Control CHOL CHOL+EECP

**p-NF/NF expression level (% of Control)**

CHOL CHOL+EECP

**IKB protein level (% of control)**

Control CHOL CHOL+EECP

- Yellow bars: phospho-NF/actin
- Red bars: Total-NF/actin
Effects of EECP on Vascular Endothelial Cell Morphology

Scanning Electron Micrographs

- The luminal surface was covered with many adherent cells.
- The endothelial cells were in disarray.
- Less cellular adherence
- Endothelial cells align parallel to direction of blood flow

Circulation 2007;116:526-534)
Enhanced External Counterpulsation

Clinical Outcomes

Angina Pectoris
Improve Exercise Capacity and Stress Radionuclide Perfusion

**Exercise Time (Bruce Protocol)**

N=18 refractory angina pts

<table>
<thead>
<tr>
<th></th>
<th>Pre-EECP</th>
<th>Post-EECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration, mean (min)</td>
<td>8 min 8 sec ± 42 sec</td>
<td>9 min 43 sec ± 46 sec</td>
</tr>
<tr>
<td>Increase in Exercise time</td>
<td>95 sec</td>
<td></td>
</tr>
</tbody>
</table>

P<0.005

Pre-EECP: 8 min 8 sec ± 42 sec
Post-EECP: 9 min 43 sec ± 46 sec
Increase in Exercise time: 95 sec

67% showed complete resolution
11% with partial resolution and
22% no change

Am J Cardiol. 1992;70:859-862.

Perfusion & Exercise Capacity in Chronic Stable Angina

Group 1 (4-center, 97 pts)

Same Level Exercise
Pre & Post EECP

- Stress Radionuclide Perfusion
  - 83% had significant improvement
  - 17% no change
  - 0% worse RN
- Double product unchanged

Group 2 (3-center, 78 pts)

Maximal Exercise
Pre & Post EECP

- Improved exercise duration
  - 6’ 37” → 7’25” (p<0.0001)
  - Increased 48 sec
- Stress Radionuclide Perfusion
  - 54% improved RN perfusion
  - 42% no change
  - 8% worse
- Double product unchanged

7-centers, 175 Patients

Am J Card 2002;89:822-824
Changes in Time to Exercise-induced ST-segment Depression

Adjusted change of mean Exercise Duration from baseline

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=58)</th>
<th>EECP (n=57)</th>
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<tbody>
<tr>
<td><strong>26 sec</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>p = 0.0279</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>42 sec</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p = 0.0004</strong></td>
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Changes in Time to Exercise-induced ST-segment Depression

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=56)</th>
<th>EECP (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-4 sec</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p = ns</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>37 sec</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>p = 0.0016</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MUST-EECP**
randomized, blinded and controlled (sham) study

J Am Coll Cardiol 1999;33:1833-40
Distribution of patients in Canadian Cardiovascular Angina Class (CCS)

Data from Clinical Consortium on 1st 2,289 patients in US

Change in Canadian Cardiovascular Society Classification

N=2,289 patients

Improved 3 Classes
22.0% (From Class IV to Class I)

Improved 2 Classes
39.5% (From Class IV to Class I or II from Class III to Class I)

Improved 1 Class
73.4% (From Class IV to Class I, II or III from Class III to Class I or II from Class II to Class I)

% of Patients improved after EECP Treatment

EECP Dosing: Exercise Capacity
Results of a randomized sham control study

Exercise Time
- Treadmill Exercise Time (sec)

Peak Time to Angina
- Peak Time to Angina (sec)

Peak Oxygen Uptake
- Peak Oxygen Uptake (ml/kg/min)

Modified Naughton protocol

EECP (N=28)  Sham Control (N=14)

Am J Cardiol 2011;107(10):1466-1472
EECP Dosing: Changes in Angina
Results of a randomized sham control study

**Canadian Cardiovascular Society Class**

*EECP (N=28)  
Sham Control (N=14)*

Am J Cardiol 2011;107(10):1466-1472
International EECP Patient Registries (IEPR)

- IEPR data is collected by the Epidemiology Data Center of the University of Pittsburgh to determine the patterns of use, safety and efficacy of EECP for a period of 3-years post treatment.

- **IEPR-1:** 5,056 patients from Jan 1998 to July 2001 from 119 US and 21 International sites with 3-year follow-up.

- **IEPR-2:** 2,917 consecutive patients from Jan 2002 to Oct 2004 from 95 US sites with 2-year follow-up.

- Entry criteria: patient gave consent and underwent at least 1 hr of EECP treatment.

- Data collected: Patients’ demographics, medical history, CAD status, quality of life, CCS Classification, medication, angina frequency and adverse clinical events before EECP, post EECP, and during follow-up period. IEPR-2 also recorded NYHA class, number of hospitalizations for heart failure patients, Duke Activity Status Index, and responses to the Kansas Cardiomyopathy Questionnaire.

Baseline characteristics of Patients in the IEPR

<table>
<thead>
<tr>
<th>Demographic</th>
<th>N=7,973</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)±SD</td>
<td>67.0 ±10.8</td>
</tr>
<tr>
<td>Men (%)</td>
<td>75</td>
</tr>
<tr>
<td>Systolic Hypertension (%)</td>
<td>75</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>84</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>43</td>
</tr>
<tr>
<td>Non-cardiac vascular disease (%)</td>
<td>34</td>
</tr>
<tr>
<td>Prior Smoker (%)</td>
<td>61</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factors at Baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since CAD diagnosis (years)</td>
<td>11 ± 9</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>69</td>
</tr>
<tr>
<td>Multivessel CAD (%)</td>
<td>80</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>31</td>
</tr>
<tr>
<td>Average LVEF %</td>
<td>47 % ± 14</td>
</tr>
<tr>
<td>Prior PCI or CABG (%)</td>
<td>87</td>
</tr>
</tbody>
</table>

Distribution of Canadian Cardiovascular Society Class

% in each CCS Class

86% in Class III/IV

Mean # of angina episodes/week 10 ± 14

2-Year after EECP for stable Angina Pectoris

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post</th>
<th>2-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>1,097</td>
<td>1,078</td>
<td>574</td>
</tr>
<tr>
<td>% improved ≥ 1 class*</td>
<td>73.0</td>
<td>74.9</td>
<td></td>
</tr>
<tr>
<td>Angina episodes/wk*</td>
<td>11±13</td>
<td>3 ±7</td>
<td>6 ±10</td>
</tr>
<tr>
<td>nitroglycerin use/wk†</td>
<td>10 ±14</td>
<td>6 ±8</td>
<td>8 ±13</td>
</tr>
</tbody>
</table>

*p<0.001 †p<0.01: Post and 2-year vs baseline

Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>During EECP</th>
<th>Cum 2-Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>0.3</td>
<td>8.5</td>
</tr>
<tr>
<td>MI (%)</td>
<td>0.9</td>
<td>8.9</td>
</tr>
<tr>
<td>HF exacerbation (%)</td>
<td>2.4</td>
<td>11.7</td>
</tr>
<tr>
<td>PCI/CABG (%)</td>
<td>0.9/0.2</td>
<td>11.0/5.2</td>
</tr>
<tr>
<td>Event-free Survival (%)</td>
<td>92.8</td>
<td>40.8</td>
</tr>
</tbody>
</table>
Diabetic Patients With Severe Angina
Immediately post EECP and 1-year follow-up

Canadian Cardiovascular Society
Angina Class III/IV

% of Patients Responding

<table>
<thead>
<tr>
<th></th>
<th>CCS Class III</th>
<th>CCS Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-EECP</td>
<td>87.6%</td>
<td>29.9%</td>
</tr>
<tr>
<td>Post-EECP</td>
<td>57.7%</td>
<td>22.7%</td>
</tr>
<tr>
<td>1-Year</td>
<td>27.1%</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

Episodes of Angina/Week

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-EECP</td>
<td>8.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Post-EECP</td>
<td>2.4</td>
<td>2</td>
</tr>
<tr>
<td>1-Year</td>
<td>3.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

➢ 72% of non DM and 69% of DM had at least 1 CCS class reduction (p=NS)
➢ Of those who improved post EECP, angina reduction maintained in 75.7% of non DM and 68.4% DM patients at 1-year

Am Heart J 2003;146:453-8
Change of CCSC and QoL and Exercise Duration in 50 refractory angina patients

Canadian Cardiovascular Society Classification

- Class I
- Class II
- Class III
- Class IV

Quality of Life SF36

- % in each CCSC
- p<0.001 Pre vs Post and Pre vs 1Year, p=0.229 Post vs 1Year

Exercise Test Duration

- seconds
- p<0.001
- p=0.087

Change of Ejection Fraction and Left Ventricular Dimensions in 50 refractory angina patients

**Ejection Fraction**

- Pre-EECP
- 1-Mo Post
- 1 Year

**Left Ventricular Dimensions**

- End Diastole
- End Systole

- Pre-EECP vs Post: $p=0.016$
- PRE-EECP vs 1 Year: $p=0.038$
- Pre-EECP End Diastole vs Post and 1 Year: $p=0.031$
- Pre-EECP End Systole vs Post and 1 Year: $p=0.032$

### Results in selected groups of patients from IEPR

<table>
<thead>
<tr>
<th>Population</th>
<th>%e</th>
<th>% improved</th>
<th>Follow-up</th>
<th>Adverse Events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly ≥ 80 years (n=249)</td>
<td>8%</td>
<td>76%</td>
<td>6-mo: 81% Maintained</td>
<td>HF exacerbation compared w younger</td>
<td>Am J Geriatric 2003;12</td>
</tr>
<tr>
<td>Diabetes (n=665 vs 867 no D)</td>
<td>43%</td>
<td>69%</td>
<td>1-year 72% maintained</td>
<td>17% MACE* vs 15% no diabetes</td>
<td>Am Heart J 2003;146</td>
</tr>
<tr>
<td>Obesity BMI &gt; 30 kg/m² (n=1120)</td>
<td>41%</td>
<td>Same as normal 76%</td>
<td>NA</td>
<td>increase from 2.9% to 4.8% from lowest to highest BMI</td>
<td>AM Heart J 2006;151</td>
</tr>
<tr>
<td>Left Main Disease (n=431 w prior CABG, n=53 w/o CABG)</td>
<td>20%</td>
<td>74% w/o LMD; 75% w prior CABG 65% w/o prior CABG</td>
<td>8-mo: Continued to improve</td>
<td>11% w/o LMD 16% w prior CABG 24% w/o CABG</td>
<td>Clin Cardiol 2004;27</td>
</tr>
<tr>
<td>Milder: CCS II (n=112)</td>
<td>8%</td>
<td>61% in CCS II vs 78% in CCS III/IV</td>
<td>2-yrs: 70% maintained vs 81%</td>
<td>26% in CCS II vs 30% in III/IV</td>
<td>Clin Cardiol 2006;29</td>
</tr>
<tr>
<td>w/o prior PCI/CABG (n=215)</td>
<td>5%</td>
<td>75% vs 73% with prior PCI/CABG</td>
<td>6-mo: 89% maintained vs 84%</td>
<td>6.3% vs 11% with prior PCI/CABG</td>
<td>Cardiology 2003;100</td>
</tr>
<tr>
<td>History Heart Failure (n=548)</td>
<td>28%</td>
<td>68%</td>
<td>6-mo: 85% maintained</td>
<td>14% vs 9% w/o HF</td>
<td>Cardiology 2001;96</td>
</tr>
<tr>
<td>LV dysfunction (EF≤35%, n=363)</td>
<td></td>
<td>77%</td>
<td>2-year: maintained</td>
<td>2% during therapy, 30% at 2-year</td>
<td>Am J Cardiol 2006;97</td>
</tr>
<tr>
<td>Systolic HF (n=355) vs diastolic HF (n=391)</td>
<td></td>
<td>72% in both groups</td>
<td>1-yr: 76% S and 78% D maintained</td>
<td>24% in both groups</td>
<td>J Cardiac Failure 05;11</td>
</tr>
</tbody>
</table>

*MACE: major adverse cardiovascular events = death/MI/CABG/PCI
Enhanced External Counterpulsation

Clinical Outcomes

Heart Failure
Heart Failure Facts

- 5.8 million people in the United States have heart failure.
- 22-26 million globally. About 2 million worldwide and 670,000 people in US are diagnosed with it each year.\(^1\)
- About one in five people who have heart failure die within one year from diagnosis.\(^1\)
- Heart failure was a contributing cause of 282,754 deaths in 2006.\(^1\)
- In 2010, heart failure will cost the United States $39.2 billion.\(^1\) This total includes the cost of health care services, medications, and lost productivity.

---

Pathophysiological features of Heart Failure

Myocardial Injury
CAD, Structural, Diabetes, Hypertension

Decrease Cardiac output

Endothelial Dysfunction

Neurohormonal: RAS, endothelin Activation

Remodeling: Hypertrophy, fibrosis

Heart Failure Disease Progression

Morbidity and Mortality

CAD: Coronary Artery Disease
RAAS: Renin, Angiotensin, System
EECP Improves the Major Pathophysiologic Features Associated with Heart Failure

EECP improves coronary perfusion

EECP improves exercise capacity, QoL

EECP increases SV and CO

EECP increases contractility

EECP improves exercise capacity, QoL

EECP increases exercise capacity, QoL

EECP decreases plasma and tissue Renin, Ang II

EECP improves Exercise capacity, QoL

EECP improves Exercise capacity, QoL
There is no known cure for HF. Pharmacotherapy currently is the standard of care to alleviate symptoms and slow HF progression. Cardiac resynchronization Therapy (CRT) with or without implantable cardioverter defibrillators (ICD), for 15% of HF patients with QRS Prolongation. Left ventricular Assist Device/Cardiac Transplantation.

Novel therapeutic modalities are needed to act in concert with pharmacotherapy in HF, as optimal pharmacotherapy alone still leaves a substantial portion of HF patients with significant symptoms, high hospitalization rate and a shortened survival.

1 Educational Content from the Heart Rhythm Society website: www.HRSonline.org
EECP in Ischemic Cardiomyopathy

Using Impedance cardiograph

*p < 0.05

Cardiac Power
SVR
Cardiac Index
Stroke Volume
Double Product

*EF > 35%
*EF < 35%

Lawson et al. J Cardiac Failure 2002;8:S146
Change in Left Ventricular Ejection Fraction
in 25 patients with refractory angina

EECP increases 6-minute walking distance

Baseline: 653
Post-EECP: 1025
1-year follow up: 1040

Feet

Baseline: 968
Post-EECP: 1181

p<0.001

47 refractory angina patients 61±8 years old
Kumar: Am J Therapeutics 2009;16;116-118

16 refractory angina patients 56±11 years old
Ahmed: J Pakistan Med Assoc 2010;60(8);692-694
CAD Patients with History of CHF

Effects of EECP on CCS Anginal Class

Without CHF (N=1,400)

With CHF (N= 548)

Pre-EECP 63% of patients in Class III/IV

6-month post-EECP 14% of patients in Class III/IV

Pre-EECP 86% of patients in Class III/IV

6-month post-EECP 33% of patients in Class III/IV

Cardiology 2001;96:78-94
2-year follow-up for Patients with LVD (EF ≤35%)

**Baseline (N=363)**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67±11</td>
</tr>
<tr>
<td>Male</td>
<td>78</td>
</tr>
<tr>
<td>History of CHF (%)</td>
<td>61</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>70</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>72</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>85</td>
</tr>
<tr>
<td>Average EF %</td>
<td>28±7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>78</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45</td>
</tr>
<tr>
<td>Noncardiac VD</td>
<td>35</td>
</tr>
<tr>
<td>History Heart Failure</td>
<td>61</td>
</tr>
<tr>
<td>Not Candidates for CAGB/PCI</td>
<td>93</td>
</tr>
</tbody>
</table>

**Major Adverse Cardiovascular Events**

<table>
<thead>
<tr>
<th>Major Adverse Cardiovascular Events</th>
<th>During EECP</th>
<th>2-year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>0.8</td>
<td>17.4</td>
</tr>
<tr>
<td>MI (%)</td>
<td>0.3</td>
<td>6.5</td>
</tr>
<tr>
<td>PCI / CABG (%)</td>
<td>0.8/ 0.3</td>
<td>9.5 / 3.3</td>
</tr>
<tr>
<td>MACE* (%)</td>
<td>1.9</td>
<td>30</td>
</tr>
<tr>
<td>CHF Exacerbation (%)*</td>
<td>3.3</td>
<td>19</td>
</tr>
</tbody>
</table>

* MACE = Death/M/PCI/CABG

- 77% of patients improved >1 angina class,
- 8% had no angina post treatment (p<0.001 baseline vs post-EECP)

- 93% in Class III/IV pre-EECP
- 55% of patients had sustained improvement in angina class at 2-year follow-up
- 2-year survival rate was 83%

Am J Cardiol 2006; 97(1):17-20
PEECH™ Trial
Prospective Evaluation of EECP in Congestive Heart Failure

- 187 patients randomized to EECP therapy plus optimal medical therapy compared to optimal medical therapy alone
- 29 centers participating including Cleveland Clinic, Scripps Clinic, Thomas Jefferson and UCSD
- Co-Primary endpoints at six months following treatment (90% Power)
  - Exercise Tolerance: % of patients with 60 second increase from baseline
  or
  - Peak VO₂: % of patients with 1.25 ml/min/kg increase from baseline
- Blinding: blinded central core lab evaluated exercise data; blinded investigators performed subject evaluations; patients not blinded
- Secondary endpoints: Change in exercise duration and peak VO₂, change in NYHA class, change in Quality of Life

J Am Coll Cardiol 2006;48:1198-1205
PEECH: Primary Endpoints

Prospective Evaluation of Enhanced External Counterpulsation (EECP) in Heart Failure

**Exercise Duration**
- Increase ≥ 60 sec from baseline
  - EECP: 35.4% (N=93)
  - Control: 25.3% (N=94)
  - p=0.016

**Peak VO₂**
- Increase ≥ 1.25 mL/kg/min from baseline
  - EECP: 22.8% (N=93)
  - Control: 24.1% (N=94)
  - p=NS

% responders at 6-month follow-up

J Am Coll Cardiol 2006;48:1198-1205
PEECH: Secondary Endpoints

Change in Exercise Duration from Baseline (sec)

1 Week 3 Months 6 Months

EECP: 26.4 p=0.01 34.5 p=0.01 24.7 p=0.01

Control: -5.5 -7 -9.9

Change in Peak VO₂ from Baseline (mL/kg/min)

1 Week 3 Months 6 Months

EECP: 0.1 p=0.07 0.2 p=NS 0.3 p=NS

Control: -0.4 -0.4 -0.6

Note: Error bars represent standard error

J Am Coll Cardiol 2006;48:1198-1205
PEECH: Secondary Endpoints

**Improvement in NYHA Class**

<table>
<thead>
<tr>
<th>Time</th>
<th>EECP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td>33.3</td>
<td>11.4</td>
</tr>
<tr>
<td>3 Months</td>
<td>31.6</td>
<td>12.2</td>
</tr>
<tr>
<td>6 Months</td>
<td>31.3</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Significance levels: p<0.01, p<0.02, p<0.001

**Improvement in Quality of Life**

Assessed by Minnesota Living with HF

<table>
<thead>
<tr>
<th>Time</th>
<th>EECP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td>-8.9</td>
<td>-3.4</td>
</tr>
<tr>
<td>3 Months</td>
<td>-7.1</td>
<td>-2.9</td>
</tr>
<tr>
<td>6 Months</td>
<td>-3.7</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

Significance levels: p=0.01, p=0.01, p=NS

J Am Coll Cardiol 2006;48:1198-1205

% Patients With Improvement in NYHA Class

After EECP Treatment
Subgroup Analysis: Age ≥ 65 years with EF ≤ 35%

% Subjects Who Met Threshold

<table>
<thead>
<tr>
<th>Condition</th>
<th>EECP</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Duration Increase ≥ 60 sec from baseline</td>
<td>35.1% (N=37)</td>
<td>25% (N=44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak VO₂ Increase ≥ 1.25 mL/kg/min from baseline</td>
<td>29.7% (N=37)</td>
<td>11.4% (N=44)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

% responders at 6-month follow-up

EECP: 35.1% (N=37) vs Control: 25% (N=44) (p=0.008)

EECP: 29.7% (N=37) vs Control: 11.4% (N=44) (p=0.017)

Congestive Cardiac Failure: 2006, Nov-Dec, 307-311
Subgroup: Age ≥ 65 years (secondary end-points)

Change in Exercise Duration from Baseline (sec)

- 1 Week: EECP=23 sec, Control=6 sec, p=0.07
- 3 Months: EECP=52.2 sec, Control=42.1 sec, p=0.004
- 6 Months: EECP=30 sec, Control=27 sec, p<0.001

Change in Peak VO₂ from Baseline (mL/kg/min)

- 1 Week: EECP=0.1 mL/kg/min, Control=-0.8 mL/kg/min, p=0.09
- 3 Months: EECP=0.3 mL/kg/min, Control=-1.1 mL/kg/min, p=0.02
- 6 Months: EECP=-0.2 mL/kg/min, Control=-1.1 mL/kg/min, p<0.001

Baseline exercise time: EECP=581 sec vs OPT=552 sec

Note: Error bars represent standard error.
PEECH: Subjects with Ischemic Etiology

Change in Exercise Duration

- Change from Baseline (sec)
  - 1 Week: 24.6 (EECP), -16.7 (Control)
  - 3 Months: 34.2 (EECP), -17.3 (Control)
  - 6 Months: 20.6 (EECP), -25.8 (Control)

- Change from Baseline (sec)
  - 1 Week: p=0.007
  - 3 Months: p=0.017
  - 6 Months: p=0.010

Change in Peak VO2

- Change from Baseline (mL/kg/min)
  - 1 Week: 0.2 (EECP), -0.7 (Control)
  - 3 Months: 0.0 (EECP), -0.4 (Control)
  - 6 Months: -0.3 (EECP), -0.9 (Control)

- Change from Baseline (mL/kg/min)
  - 1 Week: p=0.07
  - 3 Months: p=NS
  - 6 Months: p=NS

N= 53 (EECP) vs. 54 (Control)

Feldman AM, et al. presented at ACC 2005
**PEECH: Subjects with Ischemic Etiology**

**Improvement in NYHA Class**

- **1 Week:**
  - EECP: 37.0
  - Control: 12.7
  - Improvement: 34.3

- **3 Months:**
  - EECP: 34.5
  - Control: 12.3
  - Improvement: 32.2

- **6 Months:**
  - EECP: 36.4
  - Control: 15.5
  - Improvement: 30.9

**p-values:**
- 1 Week: p=0.004
- 3 Months: p=0.025
- 6 Months: p=0.026

**Minnesota Living with HF**

- **1 Week:**
  - EECP: -8
  - Control: -1.1

- **3 Months:**
  - EECP: -6.5
  - Control: -1.5

- **6 Months:**
  - EECP: -4

**N:**
- 54 (EECP) vs. 55 (Control)

Fieldman AM, et al. presented at ACC 2005
### Cost effectiveness

<table>
<thead>
<tr>
<th></th>
<th># HF patients</th>
<th>Total # Hospital Visits</th>
<th>Average Cost per Hospital Visit</th>
<th>Total Cost to Healthcare System /1,000 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ECP</td>
<td>1,000</td>
<td>3,000*</td>
<td>$5,456</td>
<td>$16,368,000</td>
</tr>
<tr>
<td>After ECP</td>
<td>1,000</td>
<td>500**</td>
<td>$5,456</td>
<td>$2,728,000</td>
</tr>
</tbody>
</table>

**Reduction in hospitalization costs after treated with ECP**

$13,640,000

**Cost to treat with ECP**

$3,640,000

**Annual savings to healthcare**

$10,000,000

**Saving per patient**

$10,000

*Average # of hospital visits before ECP over 12 months is 3.6

**Average # of hospital visits after ECP over 12 months is 0.5

### Potential Cost Savings Scenario

(Reduction in average cost of hospitalizations)
Analysis of Cost due to Heart Failure

- The estimated direct and indirect cost of HF in US for 2009 in hospitalization cost is $37.2 billion

- Reduction of 60-80% of the estimated direct and indirect cost of HF in US for 2009 in hospitalization cost would be $22.3 to $29.8 billion

- 23-25% of index heart failure admission required readmission with 30-day, 50% within 90-day

- Readmission cost consumes 30% of overall inpatient cost

- Objectives: EECP therapy reduced 30% initial hospitalization and 40% readmission, saving:
  - Initial hospital cost $4.7 billion to $6.3 billion
  - Readmission cost $2.7 billion to $3.6 billion
FDA Clearance for EECP® Therapy

- March 1995
  - Vasomedical first receives 510(k) clearance to bring EECP® therapy to market for the treatment of stable and unstable angina, acute myocardial infarction and cardiogenic shock

- June 2002
  - Clinical indications expanded to include congestive heart failure

Current clinical indications include use in the treatment of patients with

- Congestive heart failure
- Stable or unstable angina pectoris
- Acute myocardial infarction
- Cardiogenic shock
Patients Selection

FDA Labeling for EECP

**Intended Use**
- stable or unstable angina pectoris
- congestive heart failure
- acute myocardial infarction
- cardiogenic shock

**Contraindications**
- 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

Current Clinical Criteria

**Indications**
- CCS class II-IV angina Pectoris refractory to medical therapy and revascularization
- NYHA or CCS Class II-III heart failure

**Contraindications**
- 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
EECP Treatment Protocol

- **Standard Treatment Time**
  - 5 daily 1 hour treatments per week over 7 weeks for a total of 35 hours or
  - 2 x 1 hours daily over 3½ weeks for 35 hours total

- **Extension**
  - 7% from IEPR-2 had extended their 35 hours by 10.3 ± 9.8 hours because of persistent angina (67%), patient’s preference (41%), physician’s (40%)
  - Extension is safe and patients continued to benefits with significant incremental improvement in symptoms and functional class

- **Repeat Therapy**
  - 18% of the patients having completed their initial course of 35 hours of EECP undergo retreatment within 2 years
  - Common reasons for retreatment are recurrent angina, persistent angina
  - About 13% of the patients failed to complete their initial 35 hours course of EECP because of patient’s choice and adverse clinical events
  - 30% of those who failed returned within 1 year for retreatment
  - At retreatment, patients realized a benefit similar to patients who respond to a first course, with 70% improved by at least one CCS angina class, decreased angina episodes and nitroglycerin use.

Issues in EECP Therapy

- **Hemodynamic Augmentation**
  - Evaluated by ratio of peak or area of diastolic wave to systolic wave (D/S)
  - Older, female sex, hypertension, non-cardiac vascular disease, current smoker, multivessel CAS, HF, LVD, previous CABG or EECP, higher CCS class, non-candidacy for revascularization are factors associated with lower diastolic augmentation
  - Higher (D/S) ratio associated with improved response to EECP, less HF exacerbation, unstable angina, more reduction of CCS class, better QoL
  - Patients with lower (D/S) ratios achieve symptomatic benefits with EECP

- **Atrial Fibrillation**
  - Only 3.2% of patients in IEPR-2, with average beats of 50-90/min
  - Similar EECP therapy completion, benefits at 6-month except all-cause mortality and hospitalization for HF
  - Frequent irregular ectopy with high HR (>100) or low HR (<50) should delay EECP until rate control has been achieved

- **Pacemaker and Defibrillators**
  - 10% of IEPR-2 patients, with similar EECP completion, benefits and adverse events as those without implantable devices
  - Patient’s motion during EECP may lead rate-adaptive pacemakers to trigger a paced tachycardia and should be reprogrammed off.
Summary of basic and clinical effectiveness

- **Mechanisms of action**
  - Increase blood flow to during EECP treatment
  - Increase angiogenesis to ischemic tissue
  - Improve endothelial functions
  - Control neurohormonal factors

- **Clinical evidence on the safety and effectiveness in treating patients with angina pectoris and heart failure**
  - Improve exercise capacity
  - Improved cardiovascular functional class
  - Improve perfusion to ischemic regions of the myocardium
  - Improve quality of life
  - Reduce hospitalization and morbidities and mortality
General recommendations for Evaluating patients

- Patients should undergo a cardiovascular evaluation to determine the optimum medical management, risk factor modification, and revascularization options.

- Stress radionuclide perfusion before and after EECP useful.

- Recent Echocardiogram to investigate valvular disease for patients with heart murmur.

- Patients with heart failure should be assessed to make sure they are not decompensated.

- Patients with atrial fibrillation should be rate controlled and anticoagulated (with INR ≤ 3.0).
EECP: Future Directions

- Syndrome X
- Reduction of rehospitalization for heart failure patients
- Effective for renal failure patients, diuretic resistant patients, adjunct to hemodialysis
- STEMI as an adjunct to facilitate reperfusion, stabilization, particularly for RV infarcts
- Prevention progression of disease as a primary and secondary vasculoprotective therapy
Causes of Death in People With Diabetes

- Ischemic heart disease: 40%
- Other heart disease: 15%
- Diabetes: 13%
- Malignant neoplasms: 13%
- Cerebrovascular disease: 10%
- Pneumonia/influenza: 4%
- All other: 5%

The cellular basis for dysfunction in Diabetes

Hyperglycemia

- Oxidative stress

Advanced glycosylation end products

- Activation of protein kinase C

Lipid peroxidation

Endothelial Dysfunction

- Reduce Vaso-relaxation nitric oxide

- Reduce flow-mediated vasodilatation

- Increase arterial stiffness

- Increase thrombosis/leukocyte adhesion

Plaque ← Atherogenesis
Myocardial perfusion in Patient with Syndrome X

cardiovascular magnetic resonance

- 68-year old woman with disabling angina
- ST-segment depression on exercise stress Test, normal angiogram

Pre-EECP
Inferior and septal subendocardial perfusion abnormality with (arrows)

Post-EECP
Both resting and stress perfusion scans are normal
Diabetics carry the same cardiovascular risk as nondiabetics with a prior myocardial infarction.

A population Study of 3.3 Million People in Denmark

Follow for 5 yrs (1997-2002) Cox proportional-hazard Ratio for cardiovascular death:
- 2.42 for D w/o MI
- 2.44 for non-D with MI relative to non-D w/o MI
EECP: meeting the unmet needs in the treatment of diabetic cardiovascular disease

- Diabetic patients with coronary artery disease patients are known to have poor outcomes after coronary bypass and percutaneous coronary intervention*

- Diabetics have accelerated diffuse macro and microvascular disease

- Invasive revascularization may open or bypass occluded macrovascular conductive vessel, but not microvascular resistive vessels

- EECP enhances development of microvasculature, collateral and improve endothelial cell function

STEMI- RESCUE

STEMI Reperfusion Enhanced Simply with Clot Lysis and Use of Enhanced External Counterpulsation

[Bar charts showing time to reperfusion and salvage index for EECP + Lytic and Lytic treatments.]
EECP: Hemodynamic to Pleiotropic Effects

Acute Hemodynamic Effects

- Systolic Blood Pressure ↓
- Coronary Perfusion Pressure/Flow ↑
- Venous Return ↑

Cardiac Effects

- Cardiac workload ↓
- Myocardial Perfusion ↑
- Stroke Volume ↑
- Cardiac Output ↑

Improved Endothelial Function

- Nitric oxide ↑, Endothelin ↓
- Flow mediated dilation ↑
- Endothelial Progenitor cell ↑

Arterial Wall Stiffness ↓
Vascular Tone & Function ↑

Angiogenesis ↑
Collateral flow index ↑
VEGF, HGF, FGF ↑

Inflammatory Cytokines ↓
Vascular Adhesion Molecules ↓

Downregulation RAAS

Atherosclerosis ↓

Neurohumoral Regulation

Shear Stress

Clinical Benefits

- Functional Class ↑
- Exercise Capacity ↑
- Quality of Life ↑
- Exercise Capacity ↑
- Quality of Life ↑
- Exercise Capacity ↑
- Quality of Life ↑