The challenge of refractory angina

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Mr. Francesco’s short history

• Man, 68 years old
• Acute inferior MI in 1996
• Angina episodes after MI
• Due to recurrences of anginal symptoms

In a 16-year period the patient underwent:
- 23 coronary angiographies
- 2 CABG interventions
- 23 PCIs (18 with stent implantation)
- 5 hospital admissions in the last year
Mr. Francesco’s last CAG

- Stenosis 60% of LAD in the middle tract with distal subocclusion; occlusion of D1 branch
- Stenosis 60% of CX in the middle tract, with occlusion of OM1 branch
- Intermediate CA: occluded
- RCA: proximal stenosis 70%
- Critical stenosis of PL branch
- IVP branch: occluded
- Venous grafts on IVP and D1 occluded
- LIMA on LAD occluded
Refractory angina

- Attacks of angina pectoris that limit or make impossible ordinary daily activities of the patient (CCS class III-IV)
- Optimal medical therapy
- Unsuitability for both percutaneous and surgical revascularization procedures
Refractory angina

What to do

???
Refractory angina

Prevalence

Incidence

???
Refractory angina pectoris

Norwegian Randomized Trial on TMLR

Aaberge L, JACC 2000;35:1170-7

24 pts /milion people /year

Epidemiology Of Refractory Angina (ERA)

Mannheimer C, Personal communication

2.1% of patients admitted to ER for angina
Prevalence of refractory angina

- CCS angina class $\geq 2$
- No recent (<3 weeks) AMI
- Evidence of myocardial ischemia

59 out of 500 patients (11.6%) unsuitable for coronary revascularization

Mukherjee D, AJC 1999;84:598-600
Prevalence of refractory angina

- Stable angina, CCS class II-IV
- Obstructive CAD
- No recent (<3 months) ACS

48 out of 427 patients (11.2\%) unsuitable for coronary revascularization

Lanza GA 2009, unpublished
ITA-SCS trial

ITA-SCS1 NCT00121654 (https://register.clinicaltrials.gov)

39 refractory angina patients

6 centers
4.5 years

25 enrolled patients

14 patients excluded
- 4 refusal to participate
- 2 severe clinical conditions
- 8 insufficient angina attacks

1.44 pts/yr/center
Refractory angina
Prevalence/incidence

• The exact prevalence and incidence of refractory angina is unknown at present
• Appropriately prospective designed studies should be carried out to clarify this point
• Prevalence and incidence of refractory angina might significantly depend on the threshold applied for indications to coronary revascularization
Refractory angina

Proposed treatments

- Spinal cord stimulation
- Myocardial laser revascularization
- Enhanced external counterpulsation
- Angiogenic therapy
- New drug therapies (ranolazine, ivabradine, etc…)
- Other “neural therapies” (TENS, epidural anesthesia, left stellate gangliectomy)
- Intermittent urokinase therapy
- Chelation therapy
- Shock wave therapy
- Heart transplantation
- Coronary sinus stenting
Common features of treatments for refractory angina

- Controversies about the mechanisms of their therapeutic effects
- No demonstrated favorable effects on prognosis
- Frequent limitations in published studies
- Likely relevant “placebo” component in their symptomatic effects
Treatments for refractory angina pectoris

Myocardial laser revascularization
Transmyocardial laser revascularization
## Myocardial laser revascularization

### Therapeutic mechanisms

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent channels</td>
<td>Myocardial blood perfusion through the created channels from the left ventricle cavity</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Development of new microvessels</td>
</tr>
<tr>
<td>Stress redistribution</td>
<td>Improved $O_2$ supply/demand ratio</td>
</tr>
<tr>
<td>Myocardial damage</td>
<td>Destruction of ischemic areas</td>
</tr>
<tr>
<td>Myocardial denervation</td>
<td></td>
</tr>
</tbody>
</table>
Randomized controlled trials of TMLR

• Allen KB, *NEJM* 1999;341:1029 (n=275)
• Frazier OH, *NEJM* 1999;341:1021 (n=192)
• Schofield PM, *Lancet* 1999;353:519 (n=188)
• Aaberge L, *JACC* 2000;35:1170 (n=100)
Angina improvement in TMLR trials
(12-month follow-up)
TMLR vs. maximal medical therapy for refractory angina: peri-operative mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaberge 2000</td>
<td>2/50</td>
<td>0/50</td>
<td>6.2 %</td>
<td>5.21</td>
</tr>
<tr>
<td>Allen 1999</td>
<td>11/129</td>
<td>0/129</td>
<td>31.7 %</td>
<td>3.13</td>
</tr>
<tr>
<td>Burkhoff 1999</td>
<td>1/32</td>
<td>0/32</td>
<td>6.5 %</td>
<td>2.97</td>
</tr>
<tr>
<td>Frazier 1999</td>
<td>12/111</td>
<td>0/111</td>
<td>67.8 %</td>
<td>1.68</td>
</tr>
<tr>
<td>Jones 1999</td>
<td>5/50</td>
<td>0/50</td>
<td>5.7 %</td>
<td>12.43</td>
</tr>
<tr>
<td>Schofield 1999</td>
<td>5/50</td>
<td>0/50</td>
<td>6.2 %</td>
<td>11.61</td>
</tr>
<tr>
<td>van der Sloot 2004</td>
<td>1/15</td>
<td>0/15</td>
<td>5.9 %</td>
<td>3.21</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>623</strong></td>
<td><strong>430</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>3.76</strong></td>
</tr>
</tbody>
</table>

Total events: Treatment, 37 (Control), 4 (Control)
Heterogeneity: Chi² = 2.39, df = 6 (P = 0.88); I² = 0.0%
Test for overall effect: Z = 3.11 (P = 0.0019)

**Treatment**: 6.8%
**No treatment**: 0.8%

Briones E, Cochrane Library 2009
Percutaneous myocardial laser revascularization
Randomized controlled trials of percutaneous LR

• Oosterle SN, *Lancet* 2000;356:1705 (n=221)

• Stone JW, *JACC* 2002;39:1581 (n=141)

• Salem M, *Am J Cardiol* 2004;93:1086 (n=40)

• Leon MB, *JACC* 2005;46:1812 (n=298)
Effect of percutaneous MLR on CCS angina class

Patients in CCS class III-IV (%)

Baseline 12-month FU

High dose Low dose Placebo

Leon MB, JACC 2005;46:1812
Treatments for refractory angina pectoris

Angiogenic therapy
Angiogenic factor gene transfer by viral vectors (intracoronary, intramyocardial)

Factors stimulating progenitor BMC mobilization (intravenous)

Progenitor vascular stem cells (intramyocardial)

Vascular growth factors (intracoronary, intravenous)
<table>
<thead>
<tr>
<th>Study</th>
<th>N. pts</th>
<th>Angina</th>
<th>CCS</th>
<th>NTG</th>
<th>ETT</th>
<th>MI</th>
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</thead>
<tbody>
<tr>
<td>Grines 2002*</td>
<td>79</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>+/-</td>
</tr>
<tr>
<td>Grines 2003†</td>
<td>52</td>
<td>-</td>
<td>na</td>
<td>-</td>
<td>na</td>
<td>+/-</td>
</tr>
<tr>
<td>Hedman 2003‡</td>
<td>103</td>
<td>na</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Kastrup 2005#</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Henry 2007@</td>
<td>532</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*AGENT-1 trial (intracoronary adenovirus 5-FGF4)
†AGENT-2 trial (intracoronary adenovirus 5-FGF4)
‡KAT trial (intracoronary adenovirus VEGF)
#EUROINJECT trial (percutaneous intramyocardial plasmid/CMV VEGF-A$_{165}$)
@AGENT-3 & AGENT-4 trials (intracoronary adenovirus 5-FGF4)
BMC injection and ischemic segments on SPECT

van Ramshorst J, JAMA 2009;301:1997-2004
BMC injection and CCS class

van Ramshort J, JAMA 2009;301:1997-2004
Enhanced External Counterpulsation
Enhanced External Counterpulsation

Diastole

Systole
Enhanced External Counterpulsation
Therapeutic mechanisms

- Improved endothelial function
- $\uparrow$NO, $\downarrow$ET-1 release
- Reduced oxidative stress
- Decreased peripheral resistance

Increased shear stress

- Increase in collateral circulation
- Direct endothelial stimulation
- Stimulation of VEGF production
Angina improvement in EECP registries

- At least 1 CCS class
  - Consortium (n=2,289): 77.9%
  - IEPR (n=1,427): 73.4%

- At least 2 CCS class
  - Consortium (n=2,289): 38.0%
  - IEPR (n=1,427): 39.5%

Dawson WE, Cardiology 2000;94:31-35
MUSTT-EECP trial

124 patients

Active EECP  
\[n=59\]

- Age 21-81
- CCS class I-III
- CAD evidence
- Positive ETT

“Sham” EECP  
\[n=65\]

ETT results in the MUST-EECP trial

Patients with reduction of angina episodes >50% in the MUST-EECP trial

Enhanced External Counterpulsation
Contraindications

- Heart failure / LVEF <30%
- Uncontrolled hypertension
- Aortic aneurysm / dissection
- Significant valvular aortic regurgitation
- Significant peripheral venous disease
- Severe peripheral arterial disease
- Severe chronic obstructive pulmonary disease
- Arrhythmias interfering with EECP triggering
- Recent arterial puncture
- Coagulopathy / anticoagulant therapy
## Enhanced External Counterpulsation

### Adverse events

<table>
<thead>
<tr>
<th>Condition</th>
<th>MUST-EECP</th>
<th>Consortium</th>
<th>IEPR</th>
<th>Erdling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.3</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS/UA</td>
<td>0.15</td>
<td>4.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS discomfort</td>
<td></td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abnorm</td>
<td>18.3</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Pain leg/back</td>
<td>29.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatments for refractory angina pectoris

Spinal cord stimulation
NEUROSTIMULATION SYSTEM

Epidural electrode

Impulse generator

C3-T2
Pain inhibitory substances inhibit gates in the corpus callosum (CORTEX), thalamus (THALAMUS), and dorsal neurons (C2-T2) to block pain signals from the viscera (VISCERA) and soma (SOMA) to the heart.
Spinal cord stimulation
Clinical studies on anti-ischemic effects

↓ ischemia on Ex-T

↓ ischemia on A-ECG

↓ ischemia on pacing

MBF redistribution
## Controlled trials of SCS in angina

<table>
<thead>
<tr>
<th>Study</th>
<th>N. pts</th>
<th>Angina</th>
<th>CCS</th>
<th>NTG</th>
<th>ETT</th>
<th>QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Jongste ’94*</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ESBY ’98†</td>
<td>104</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hautvast ’98</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SPiRiT ’06‡</td>
<td>68</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eddicks ’07#</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+°</td>
</tr>
</tbody>
</table>

*Including 2 studies; †Including follow-up studies; ‡Comparison with PMLR
#Cross-over placebo-controlled trial; °6-minute walking distance
Electrical Stimulation vs. By-pass

104 patients

CABG = 51
- PCI not feasible
- Indication to CABG
  - High risk
  - No prognostic benefit

SCS = 53

Mannheimer C, Circulation 1998;97:1157-63
ESBY Trial - Long-term follow-up
Nottingham Health Profile

Quality of Life

Baseline 6 months 4-5 years

CABG  SCS

P<0.001  P=NS

Ekre O, Eur Heart J 2002;23:1938-45
ESBY Trial - Long-term follow-up

![Graph showing cumulative survival over time with markers for CABG and SCS event times.]

Ekre O, Eur Heart J 2002;23:1938-45
Paresthesic area
“Placebo” controlled study of SCS in refractory angina
SCS-ITA trial

ITA-SCS1 NCT00121654 (https://register.clinicaltrials.gov)

25 implanted patients

Group PS
n=10

1-month FU

Group NS
n=8

1-month FU

Group SS
n=7

1-month FU

1 patient dead for AMI

n=12 pts

3-month FU

n=12 pts

3-month FU
Angina attacks in the 3 groups at 1 month follow-up

Lanza GA, 2010, submitted
CCS angina class and QoL in the 3 groups at 1 month follow-up

- CCS angina class and EuroQoL VAS in the 3 groups at 1 month follow-up

- p for changes = 0.02
- p for changes = 0.05

Lanza GA, 2010, submitted
Angina attacks in patients with PS or SS at 3-month FU

No. angina attacks

Basal

3-month FU

p for changes = 0.002

Lanza GA, 2010, submitted
CCS angina class and QoL in patients with PS or SS at 3-month FU

- CCS angina class
- QoL

Group PS: n=12
Group SS: n=12

- Basal
- 3-month FU

p for changes = 0.46

- EuroQoL VAS

Lanza GA, 2010, submitted
Classical paraesthesic stimulation consistently more effective than “sham” stimulation, but not than subthreshold stimulation.

Intermediate results with subthreshold stimulation (“dose-related” effect).
Spinal cord stimulation

Side effects and complications

- Electrode dislodgment (15-20%)
- Subfascial or epidural hematoma
- Infections (2-3%)
- IPG dehiscence (~2%)
- IPG intolerance
- Dura mater puncture (pain)
- Anterior electrode positioning
- Incorrect electrode-extension connection
## Refractory angina patients

### Comparison of treatments

<table>
<thead>
<tr>
<th></th>
<th>Prognosis</th>
<th>Angina symptoms</th>
<th>Available</th>
<th>Costs</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MLR</strong></td>
<td>-</td>
<td>+/-(-)</td>
<td>-</td>
<td>+/-</td>
<td>--</td>
</tr>
<tr>
<td><strong>Ang-Th</strong></td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td><strong>EECP</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>SCS</strong></td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
Conclusions

• At present, in patients with refractory angina, SCS and EECP should be considered as first choice therapy

• Although the choice can be based on individual preference and experience, SCS should be preferred in presence of potential risks related to EECP
Thank you!