ENHANCING MYOCARDIAL REVASCULARIZATION - STEPWISE PROGRESS IN CLINICAL PRACTICE - From Laser to cell Therapy

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OBJECTIVE OF SURGICAL AND CARDIOLOGICAL REVASCULARIZATION

• Provide blood supply to the ischaemic myocardium
• Relief of angina, improve exercise tolerance and realize of survival benefit
• Preventing abnormal myocardial remodeling
RELATED FACTORS FOR EFFECTIVE MYOCARDIAL REVASCULARIZATION

COMPLETE MECHANICAL REVASCULARIZATION
BY PTCA OR CABG

TISSUE RIGENERATION

ANGIOGENESIS
CHIMERA OF COMPLETE MYOCARDIAL REVASCULARIZATION BY CABG OR PTCA

- Diffuse diseases
- Distal lesions
- Small coronary artery trees
- Progression of atherosclerotic lesions
Diffuse Coronary Artery Disease

Impact On Surgical Outcomes

When quantified, is a strong independent predictor of operative mortality

Incomplete revascularization due to diffuse CAD, particularly in the elderly, is an independent predictor of perioperative mortality

Incomplete revascularization is estimated to occur in 15-25% of CABG patients
INADEQUATE MYOCARDIAL REVASCULARIZATION WHICH SOLUTION?

- "RESCUE" OF OLD TECHNIQUES OF INDIRECT MYOCARDIAL REVASCULARIZATION (VINEBERG OPERATION)

- USE OF ANGIOGENETIC "TOOLS" AS TRANSMYOCARDIAL LASER REVASCULARIZATION, GROWTH FACTORS AND STEM CELLS
INDICATIONS FOR NEOANGIOGENETIC TOOLS

- **PTRM, TMR + CABG**: pts undergoing incomplete percutaneous or surgical revascularization
- **TMR + VINEBERG +/- CABG**: pts undergoing incomplete surgical revascularization, with LAD not suitable for direct standard grafting
- **TMR+PIATELETS LYSATE + BMSC ± CABG**: all previous
INDICATIONS FOR NEOANGIOGENETIC TOOLS

• PTRM, TMR ± CABG: pts undergoing incomplete percutaneous or surgical revascularization

• TMR + VINEBERG +/− CABG: pts undergoing incomplete surgical revascularization, with LAD not suitable for direct standard grafting

• TMR + PLATELETS LYSATE + BMSC ± CABG: all previous
Transmyocardial Laser Revascularization (TMR)
TMR

3 week histology demonstrating robust neoangiogenesis

Longitudinal channel - Angiogenesis

Several mm away from the channel remnant

BRDU 4x

Image courtesy of Daniel Burkhoff, M.D., Columbia Medical Center
Transmyocardial Laser Revascularization
“The Biomechanical Trigger”

Local Border Zone

Upregulation of injured myocytes
Platelet activation with growth factor release
Recruitment of intrinsic myocardial stem cells

angiogenesis

from K.B. Allen
Transmyocardial Revascularization

USA Practice Guidelines

- **Sole Therapy TMR**
  - ACC/AHA 2002: Class IIA, Grade A evidence
  - Society of Thoracic Surgeons 2003: Class I, Grade A evidence
  - ISMICS 2006: Class I, Grade A evidence

- **Adjunctive TMR when CABG alone would result in incomplete revascularization**
  - Society of Thoracic Surgeons 2003: Class IIA, Grade B evidence
  - ISMICS 2006: Class I, Grade B evidence

from K.B. Allen
INDICATIONS FOR USE OF NEOANGIOGENETIC TOOLS

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VINEBERG OPERATION

Vincente Vineberg
The Vineberg operation

LIMA harvesting and tunneling thought LV wall

Mammary artery fixation

coronary angiography six months after Vineberg
Is Vineberg operation a mad idea?

Correspondence

Vineberg operation combined with growth factor implantation

Francis Robicsek, MD, PhD. Alexander A. Fokin, MD, PhD

We read with interest the article by Pecher and Schumacher [1] and the correspondence of Johnson and associates [2] and Pecher and Schumacher [3] regarding revival of the Vineberg procedure combined with injection of angiogenic material around the implanted mammary artery. As we [4] suggested in 1999, such an arrangement likely provides a source of collaterals around the implanted mammary graft. Pecher and Schumacher [3] emphasized that the "promising results ... certainly justify increasing efforts in research, and further experimental and clinical investigations" to provide proof of the efficiency of this combined procedure.

It is our opinion that insertion of growth factors around the implantation site definitely enhances the efficiency of the Vineberg procedure and makes it applicable to patients who, because of the lack of graftable coronary arteries, are not suitable candidates for direct coronary artery bypass grafting.
Vineberg operation combined with growth factor implantation

Francis Robicsek, MD, PhD, Alexander A. Fokin, MD, PhD

Experimental evidence

It is our opinion that insertion of growth factors around the implantation site definitely enhances the efficiency of the Vineberg procedure and makes it applicable to patients who, because of the lack of graftable coronary arteries, are not suitable candidates for direct coronary artery bypass grafting.

Fig 1. Development of collaterals in the two study groups at three different times: baseline (A), 3 weeks after ameroid-induced ischemia (B), and 3 weeks after Vineberg procedure (C). (bFGF = basic fibroblast growth factor.)
Correspondence

Vineberg operation combined with growth factor implantation

Francis Robicsek, MD, PhD\textsuperscript{a}, Alexander A. Fokin, MD, PhD\textsuperscript{a}

References

TMR AND VINEBERG
OBJECTIVE

To assess feasibility, efficacy and safety of TMR combined with Vineberg operation performed in patients unsuitable for standard revascularization techniques.

To maximize the blood supply to the myocardial areas where neoangiogenesis is likely to appear after TMR treatment.

To assess the late patency of the internal mammary artery implanted.
INDICATIONS FOR USE OF NEOANGIOGENETIC TOOLS

• PTRM, TMR + CABG: pts undergoing incomplete percutaneous or surgical revascularization

• TMR + VINEBERG +/- CABG: pts undergoing incomplete surgical revascularization, with LAD not suitable for direct standard grafting

• TMR + PLATELETS LYSATE ± BMSC ± CABG: all previous
TMR plus growth factors are synergistic and result in enhanced angiogenesis beyond their individual effect

Tissue Status

The Microenvironment

- Ischemic myocardium at the border of infarct zones or hibernating myocardium can be rescued by angio/myogenesis using stem cells


- Border zones to myocardial injury create an ideal environment for regeneration of blood vessels with enhanced mitotic and cell cycle activity up to 4X compared to areas remote from non-injured heart muscle

  Anversa 2002
WHY GROWTH FACTORS FROM PLATELET LYSATE?

- A source of multiple autologous growth factors: PDGF, FGF, IGF-I/II; TGF-B
- Once applied in a wound, accelerate the tissue regenerations and repair

- Chemotaxis
- Angiogenesis
- Mitogenesis
- Synthesis
UTILIZATION OF PLATELETS CELL LYSATE (PTL lys)

As liquid solution

Solid as a patch

Addet to BMMCs
TMR + GROW FACTORS + STEM CELLS
Which Cells? From Where?

- Embryonic Stem Cells
- Umbilical Cord Blood Stem Cells

- **Autologous Bone Marrow** may be ideal since it not only provides “stem cells and precursor cells as a source of regeneration tissue but also accessory cells that support angiogenesis by producing growth factors and cytokines”

  Saigawa 2004
AUTOLOGOUS BONE MARROW AS A SOURCE FOR STEM CELLS

Multipotent Stem Cells

- Stromal Stem Cells
  - Represents 1/250K marrow Cells; decreases with age

- Hematopoietic Stem Cells
  - Represents 1/15K marrow cells; does not change with age

Isolated stem cell lines versus combined cell populations

from K.B. Allen
Current techniques require smaller autologous bone marrow aspirates (60-240 ml) from the patients iliac crest with rapid (15 min), point of care separation of bone marrow MNC using gradient centrifugation.
SURGICAL STEPS OF TMR, PLT lys (myocardial infusion and patch) AND BMMCs APPLICATION

BLOOD MARROW DRAFT: 60 ML

... AND RPM: 10000 X 3 MIN

PLATELETS LYSATE

IL LISATO PIASTRINICO

BONE MARROW STEM CELLS AND PLATELETS LYSATE
PREPARAZIONE SET PER PRELIEVO MIDOLLARE

QUALITY CONTROL
TRANSMYOCARDIAL LASER

BMMCs AND PTL lys INJECTION

.... BMMCs and PTL lys INJECTION

PLATELETS LYSATE PATCH
PATIENTS TREATED BY PTMR, CABG, PTL lys AND BMSC FROM 1998 TO 2010
Cardiothoracic and Vascular Department
SS Antonio e Biagio H - Alessandria

TOTAL EXPERIENCE
215

PTMR 110
TMR + CABG 55
TMR + VINEBERG 30
TMR PTLlys 10
TMR PTL lys BMSC 10

from 2006 to 2010
PATIENTS SELECTION

INCLUSION CRITERIA

• Evidence of viable myocardium
• Patients with diffuse CAD not amenable to CABG or PTCA ALONE
• (EF greater than 40 %)

EXCLUSION CRITERIA

• Inability to undergo a surgical procedure
• AMI within Three weeks
• Severe COPD
• Hx of life-threatening arrhythmia
## Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TMR + VINEBERG</th>
<th>TMR + PLT lys</th>
<th>TMR + PLT lys + BMSC</th>
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<tbody>
<tr>
<td>N°</td>
<td>30</td>
<td>10</td>
<td>10</td>
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<tr>
<td>AGE</td>
<td>66.7 ±/− 8.2</td>
<td>67.5 ±/− 3.7</td>
<td>62.9 ±8.2</td>
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<tr>
<td>Female Gender</td>
<td>10</td>
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<tr>
<td>Hx MI</td>
<td>16</td>
<td>7</td>
<td>4</td>
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<tr>
<td>Hx CABG</td>
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<tr>
<td>Hx PTCA</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>CCS IV</td>
<td>19</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>EF (%)</td>
<td>58.7 ±/− 10.3</td>
<td>58.8±14.9</td>
<td>44.3 ±/− 22.3</td>
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<tr>
<td>LEDVP (mmHg)</td>
<td>17.7±10.0</td>
<td>13.8±3.9</td>
<td>15.5±2.9</td>
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<tr>
<td>Euroscore Logistic</td>
<td>10.0±10.3</td>
<td>6.9±5.8</td>
<td>8.4±6.2</td>
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</table>
## CORONARY ANGIOGRAPHY

<table>
<thead>
<tr>
<th>SURGERY N° patients</th>
<th>TMR + VINEBERG (30)</th>
<th>TMR + PLT lys (10)</th>
<th>TMR + PLT lys + BMSC (10)</th>
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<tbody>
<tr>
<td>LM</td>
<td>3</td>
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<td>0</td>
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<tr>
<td>3 vessel disease</td>
<td>19</td>
<td>7</td>
<td>8</td>
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<tr>
<td>2 Vessel Disease</td>
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</tr>
<tr>
<td>1 Vessel Disease</td>
<td>1</td>
<td>1</td>
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<tr>
<td>absent LAD</td>
<td>15</td>
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<td>2</td>
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<tr>
<td>absent CX</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>absent CDx</td>
<td>9</td>
<td>3</td>
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### OPERATIVE DATA

<table>
<thead>
<tr>
<th></th>
<th>TMR + VINEBERG (30)</th>
<th>TMR + PLTYS (10)</th>
<th>TMR + PTLys + BMSC (10)</th>
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</thead>
<tbody>
<tr>
<td>CPB (min)</td>
<td>103.3 ± 25.9</td>
<td>93.8 ± 26.6</td>
<td>85 ± 28</td>
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<tr>
<td>Cross Clamp</td>
<td>50.3 ± 19.0</td>
<td>58.4 ± 28.7</td>
<td>51.8 ± 21.6</td>
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<tr>
<td>Ischaemic Time</td>
<td>34.0 ± 17.4</td>
<td>44.5 ± 14.6</td>
<td>42.7 ± 17.3</td>
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<td>Off Pump</td>
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<tr>
<td>GABG x 1</td>
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<td>1</td>
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<tr>
<td>CABG x 2</td>
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<td>4</td>
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<tr>
<td>CABG ≥ 3</td>
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<tr>
<td>NO CABG</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>TMR channels (n°)</td>
<td>29.4 ± 2.9</td>
<td>29.4 ± 2.9</td>
<td>23.4 ± 6.9</td>
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</table>
## RESULTS AND FU

<table>
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<tr>
<th></th>
<th>TMR+VINEBERG</th>
<th>TMR+PTL lys</th>
<th>TMR+PTL lys+BMSC</th>
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</thead>
<tbody>
<tr>
<td>FOLLOW UP (m)</td>
<td>120,4 ± 31,7</td>
<td>50,8 ± 9,2</td>
<td>30,7 ± 6,1</td>
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<tr>
<td>H MORTALITY</td>
<td>2*</td>
<td>0</td>
<td>1**</td>
</tr>
<tr>
<td>LATE MORTALITY</td>
<td>5***</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

* 1=LCO; 1=MOF  
** LCO  
*** (1; 4; 10; 11; 12 yrs PO) : 2 cardiac, 2 K, 1 pneumonia

<table>
<thead>
<tr>
<th></th>
<th>pre op</th>
<th>post op</th>
<th>pre op</th>
<th>post op</th>
<th>pre op</th>
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</thead>
<tbody>
<tr>
<td>CCS I</td>
<td>6</td>
<td>15</td>
<td>0</td>
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<tr>
<td>CCS II</td>
<td>6</td>
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<td>CCS III</td>
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<tr>
<td>CCS IV</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>0</td>
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</table>

pre op: preoperative  
post op: postoperative
CONCLUSIONS 1

• TRANSMYOCARDIAL LASER REVASCULARIZATION, VINEBERG OPERATIONS AND INTRAMYOCARDIAL APPLICATION OF PLATELETS LYSATE AND BONE MARROW STEM CELLS CAN BE DONE EASILY AND EFFECTIVELY IN AREAS OF ISCHAEMIC AND VIABLE MYOCARDIUM UNSUITABLE FOR CONVENTIONAL REVASCULARIZATION TECHNIQUES
CONCLUSIONS 2

- TMR AND VINEBERG OPERATION, WHEN INDICATED, AND PLATELETS LYSATE AND BONE MARROW STEM CELLS ARE ASSOCIATED WITH ACCEPTABLE OPERATIVE RISK AND MUST BE CONSIDERED FOR CORONARY RIVASCULARIZATION OR AS A USEFUL ADJUNT TO ROUTINE CABG WHEN IT CANNOT BE ADEQUATELY ACCOMPLISHED BECAUSE OF DIFFUSE CORONARY DISEASE OR LACK OF DISTAL TARGETS.