Myoblast Transplantation

Advanced Angioplasty
London, May 18, 2003
Heart Failure

Epidemiology

- High incidence (~ 500,000 per year in the U.S.)
- High mortality (40% at 1 year in Class III-IV patients)
- High costs (20 billion $/year)
Comparative Five-Year Survival Between Heart Failure and Malignancies

## Surgery for Severe Postinfarction LV Dysfunction

### Conceptual Approaches

<table>
<thead>
<tr>
<th>Objective</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement</td>
<td>Cardiac Tx/LVAD</td>
</tr>
<tr>
<td>Reshaping</td>
<td>Endoventricular patch plasty</td>
</tr>
<tr>
<td>Regeneration</td>
<td>Cellular transplantation</td>
</tr>
</tbody>
</table>
Number of Heart Transplants Reported by Year

* Numbers may be low due to delayed reporting.
Heart Transplantation
Actuarial Survival (1982-2001)

Half-life = 9.3 years
Conditional Half-life = 11.8 years

N=60,936
Effect of LVAD on Survival of Patients With End Stage Heart Failure

<table>
<thead>
<tr>
<th>Target Tissue</th>
<th>Clinical Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Routine</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>Langerhans islets</td>
<td>Investigational</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
</tr>
<tr>
<td>Retina</td>
<td></td>
</tr>
</tbody>
</table>
Cell-Based Replacement Therapy for Heart Failure

Basic Assumptions

- Relationship between the extent of infarct-related myocardial akinetic areas and the development of heart failure
- Possibility of restoring function of these areas by repopulating them with contractile cells
Cellular Transplantation

Types of Contractile Cells

- Naturally contracting cells:
  - Fetal cardiomyocytes
  - Skeletal myoblasts

- Potentially orientable towards a contractile pattern:
  - Bone marrow stem cells
  - Embryonic stem cells
Advantages of Skeletal Myoblasts

- Autologous origin
- Great expansion potential *in vitro*
- Commitment to a myogenic fate
- High resistance to ischemia
Regression of PostMI Fibrosis (Sheep Model of MI, Assessment at 4 Months)
Scar Colonization With Myotubes (4 mo. postTx)

(x100)
Hematoxylin-eosin (x300)
1-Year Histological Results

Hematein-eosin

Fast skeletal myosin (MY-32 clone)

Slow myosin (NOQ-7 clone)
Z Bands & New Satellite Cells (Sheep Model of MI, 4 mo. PostTx)
Effects of Baseline EF
2-Month Results

* $p=0.011$, # $p=0.0026$ and § $p=0.02$ vs controls

<table>
<thead>
<tr>
<th>LVEF (%)</th>
<th>Controls</th>
<th>Myoblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

** $p < 0.0001$ vs Controls

* $p = 0.0048$ vs ACEI

# $p < 0.0001$ vs ACEI

§ $p = 0.0084$ vs Myoblasts

LV EF (%)

![Graph showing LV EF (%) for different conditions](image)
Increased Contractility Following Myoblast Transplantation

1-Year Rat Studies
Emax

4-Month Sheep Studies
Systolic Velocity Gradient

$\text{Control} \quad \text{Myoblast}$

$\text{PreTx} \quad \text{PostTx}$

$p < 0.0001$

$p = 0.005$

$p = 0.006$

**$p = 0.005$
1-Year Functional Results
Echocardiography

LVEF (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Myobl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreTx</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>2 months</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>1 year</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

Legend:
- Control
- Myobl.
Myoblast Transplantation

Mechanisms of Action

1- Limitation of remodeling
2- Increase in contractility
   - Directly: Electrochemical coupling with host cardiomyocytes
   - Indirectly: Paracrine effects
In Vivo Visualization of Engrafted Myotubes

Protocol Outline
(B. Léobon, E. Audinat, S. Charpak)
- Transfection of myoblasts with green fluorescence protein
- Injection of transfected myoblasts into infarcted rat myocardium
- Microscopic examination of beating heart explants (1 mo. postTx) allowing to target grafted areas for:
  - Recording of APs and contractions
  - Assessment of coupling
Assessment of Coupling
Coupling of Cardiomyocytes
Lack of Coupling Between Host Cardiomyocytes & Engrafted Myotubes
Myoblast Transplantation

Lines of Support for a Paracrine Mechanism: Heart

- Maintenance of long-term functional benefits despite a decreased number of engrafted myotubes over time
- Reduction of collagen content in grafted scars (30 ± 2% vs 73 ± 3% in a sheep model of MI, \( p < 0.0001 \))
Myoblast Transplantation

Lines of Support for a Paracrine Mechanism: Other Organs

- **Brain**: Dopaminergic effects of cerebral tissue grafts
- **Pancreas**: Insulin secretion by transplanted Langerhans islets
- **Retina**: Cone-rod interactions
Editorial

Roads to Survival

Insulin-Like Growth Factor-1 Signaling Pathways in Cardiac Muscle

Ping H. Wang

From the Departments of Medicine and Biological Chemistry, Division of Endocrinology, Diabetes, and Metabolism, University of California, Irvine, Calif.
Cardioprotective Effects of IGF-1

Wall motion score

* $p = 0.01$

Vascularization

$p = 0.003$

Troponin I release

* $p = 0.001 \text{ vs control}$

Production of Insulin Growth Factor-1 by Human Skeletal Muscle Cells

ng/mL

Medium  Myoblasts

Medium  Myotubes

0
0,05
0,1
0,15
0,2
0,25
0,3
0,35
0,4
0,45

0
0,05
0,1
0,15
0,2
0,25
0,3
0,35
0,4
0,45

1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0

Medium  Myotubes

Medium  Myoblasts
<table>
<thead>
<tr>
<th>Country</th>
<th>Sponsor</th>
<th>Approach</th>
<th>Associated Procedure</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Hospital</td>
<td>Surgical</td>
<td>CABG</td>
<td>Completed</td>
</tr>
<tr>
<td>Poland</td>
<td>Hospital</td>
<td>Surgical</td>
<td>CABG</td>
<td>Completed</td>
</tr>
<tr>
<td>USA</td>
<td>Industry</td>
<td>Surgical</td>
<td>CABG</td>
<td>Completed</td>
</tr>
<tr>
<td>Italy/</td>
<td>Industry</td>
<td>Percutaneous</td>
<td>LVAD</td>
<td>Ongoing</td>
</tr>
<tr>
<td>The Netherlands</td>
<td></td>
<td></td>
<td>None</td>
<td>Stopped</td>
</tr>
</tbody>
</table>
Inclusion Criteria

- Impairment of LV function (≤35%)
- Postinfarction aki netic (echo + dobutamine), metabolically nonviable ($^{18}$FDG PET scan) & nonrevascularizable scar
- Need for elective CABG in ischemic & viable areas (remote from the cell-grafted scar)
Preoperative Characteristics
(10 patients)

- Male sex : 10
- Mean age (yr) : 60.3 (38-73)
- NYHA II/III/IV Class : 4/4/2
- Location of MI : anterior (6), posterior (3), postero-lateral (1)
- Age of infarct : 6.2 yr (3 mo-19 yr)
- Mean LVEF (%) : 24 ± 1 (18-31)
Myoblast Tx : Phase I Human Trial

Staging of the Procedure

- Muscular biopsy
- Cell cultures
- Cell reimplantation
Intramyocardial Injections of Cells
Basic Requirements

- Use of clinical-grade culture media and ancillary products
- Development of large-scale cell expansion procedures in GMP-certified facilities
- Set-up of appropriate quality controls
- Efficacious handling of long-distance shipment logistics
Myoblast Tx: Phase I Human Trial Feasibility

Results of Cultures

- Total number of cells produced (x $10^6$): 953 (530-1,215)
- Total number of cells injected (x $10^6$): 871 (500-1,150)
- % of myoblasts (CD56 +): 87 (67-97)
- % of viable cells (PI +): 95 (86-99)
- Biopsy/implantation interval (days): 16 (14-20)
# Phase I Clinical Trials of Autologous Skeletal Myoblast Tx: Safety

<table>
<thead>
<tr>
<th>Step</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell expansion</td>
<td>Contamination</td>
</tr>
<tr>
<td>Cell implantation</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Cell engraftment</td>
<td>Emboli</td>
</tr>
<tr>
<td></td>
<td>Oncogenicity</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
</tr>
</tbody>
</table>
### Myoblast Tx : Phase I Human Trial Safety

#### Ventricular Tachycardia (4 Patients)

<table>
<thead>
<tr>
<th>Timing (PO days)</th>
<th>Clinical symptom</th>
<th>Treatment</th>
<th>FU (mo)</th>
<th>Shocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (+ 5 mo)</td>
<td>syncope</td>
<td>AICD</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>11 (+ 9 mo)</td>
<td>dizziness</td>
<td>AICD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>dizziness</td>
<td>AICD</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>none</td>
<td>AICD</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
In Vivo Visualization of Engrafted Myotubes

Protocol Outline
(B. Léobon, E. Audinat, S. Charpak)

- Transfection of myoblasts with green fluorescence protein
- Injection of transfected myoblasts into infarcted rat myocardium
- Microscopic examination of beating heart explants (1 mo. postTx) allowing to target grafted areas for:
  ✓ Recording of APs and contractions
  ✓ Assessment of coupling
Action Potential Duration at Half-Height

- $p < 0.001$ vs muscular fiber, myotube in muscle & myotube in heart
- $p < 0.05$ vs myotube in heart

- CM: 22
- Muscular fiber: 15
- Myotube in culture: 9
- Myotube in muscle: 8
- Myotube in heart: 12

$N = 22$
Hyperpolarization

* $p < 0.001$ vs all myotube groups

** $p < 0.05$ vs myotube in heart

- CM
- Muscular fiber
- Myotube in culture
- Myotube in muscle
- Myotube in heart

$N = 22 \quad 15 \quad 9 \quad 8 \quad 12$
Specificities of Engrafted Myoblasts: Depolarizing Rebounds

N = 10/12
Specificities of Engrafted Myoblasts: Burst of Action Potentials

\[ N = 6/12 \]
Amiodarone reduces transmural heterogeneity of repolarization in the human heart.

Drouin E, Lande G, Charpentier F.
Department of Neonatology, Centre Hospitalo-Universitaire de Nantes, France.

OBJECTIVES: The present work was designed to test the effects of amiodarone therapy on action potential characteristics of the three cell types observed in human left ventricular preparations.

BACKGROUND: The electrophysiologic basis for amiodarone's exceptional antiarrhythmic efficacy and low proarrhythmic profile remains unclear.

METHODS: We used standard microelectrode techniques to investigate the effects of chronic amiodarone therapy on transmembrane activity of the three predominant cellular subtypes (epicardial, midmyocardial [M] and endocardial cells) spanning the human left ventricle in hearts explanted from normal, heart failure and amiodarone-treated heart failure patients.

RESULTS: Tissues isolated from the ventricles of heart failure patients receiving chronic amiodarone therapy displayed M cell action potential duration (404+/−12 ms) significantly briefer (p < 0.05) than that recorded in tissues isolated from normal hearts (439+/−22 ms) or from heart failure patients not treated with amiodarone (449+/−18 ms). Endocardial cells from amiodarone-treated heart failure patients displayed longer (p < 0.05) action potential duration (363+/−10 ms) than endocardial cells isolated from normal hearts (330+/−6 ms). As a consequence, the heterogeneity of ventricular repolarization in tissues from patients treated with amiodarone was considerably smaller than in the two other groups, especially at long pacing cycle lengths.

CONCLUSIONS: These findings may explain, at least in part, the reduction of ventricular repolarization dispersion and the lower incidence of torsade de pointes observed with chronic amiodarone therapy as compared with other class III agents.
Myoblast Tx: Safety Concerns

Management
- Efficacy of amiodarone prophylaxis (from biopsy to 3 mo. postTx)
- Elective ICD implantation (overlapping of cell Tx & MADIT-II patient populations)
Effects of AICD on Survival of Patients With Severe Postinfarction LV Dysfunction (MADIT II)

Assessment of Function

- Blinded review of echocardiograms
- Methodologic limitations:
  ✓ Small number of patients
  ✓ Limited period of follow-up
  ✓ Confounding effect of CABG
Functional Outcomes: Global Status

NYHA Class

PreTx: 3
PostTx: 1.5

FU: 16.8 mo. (10-22)

LVEF (%)

PreTx: 25
PostTx: 35

p < 0.0001

p < 0.05
Functional Outcomes:
Restoration of Systolic Shortening in Myoblast-Transplanted Scarred Segments

% improved

FU : 10.9 mo (5-17.5)

FU : 16.8 mo (10-22)
Echocardiographic Assessment of Myoblast Transplantation

PreTx

PostTx (6 & 21 months)
Magnetic Resonance Imaging

PreTx
13.06.2001

PostTx
20.07.2001
Myoblast Tx : Phase II MAGIC Trial

Overview of Study Design
- Randomized multicenter placebo-controlled dose-ranging trial (300 patients)
- Centralized production of cells (2 sites)
- Primary & secondary end points: Improvement in the kinetics of cell-grafted areas at 6 months (blinded echo assessment in a core lab) & MACE at 1 year
Engrafted Myotubes Into an Infarcted Human Heart
Engrafted Myotubes Into an Infarcted Human Heart
Engrafted Myotubes

Sheep Heart

Human Heart
Changes in Myosin Isoform Expression

<table>
<thead>
<tr>
<th></th>
<th>Fast</th>
<th>Slow</th>
<th>Fast &amp; Slow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human heart tissue</td>
<td>35.3%</td>
<td>32%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Human Vastus Lateralis muscle</td>
<td>55.4%</td>
<td>44%</td>
<td>0.60%</td>
</tr>
</tbody>
</table>
Myoblast Transplantation

Clinical Perspectives
- Comparison with other cell types
- Assessment of catheter-based cell delivery techniques
- Extension to nonischemic cardiomyopathies
Bone Marrow Cells

Rationale
Potential cardiomyogenic/endothelial differentiation

Advantages
- Autologous origin
- Simplicity of cell collection (bone marrow or blood)
Bone Marrow Transplantation

« Whole » Unpurified Bone Marrow (MNCs)

- Advantages: Simplicity & full exploitation of the differentiation potential of mixed cell populations
- Results: Functional benefit only if cell injections in border zones (chronic MI) or early following acute MI
- Issues:
  ✓ If injections in border zones: limited improvement
  ✓ If early postMI injections: uncertainty regarding transendothelial passage of intracoronarily injected cells
Fresh Autologous Bone Marrow Tx Protocol

Creation of MI in sheep

- Baseline echo assessment of LV function
- Aspiration of bone marrow/centrifugation
- *Immediate* reinjection of unfractionated bone marrow or culture medium (n=9/group)

Day 0

2 weeks

2 months

- Final echo assessment
- Explantation &
- Pathology
Effects of Fresh Autologous Bone Marrow Transplantation on LV Ejection Fraction

<table>
<thead>
<tr>
<th></th>
<th>PreTx</th>
<th>PostTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>p = 0.03</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>PreTx</th>
<th>PostTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>p = 0.008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of Fresh Autologous Bone Marrow Tx on Mean Systolic Velocity Gradient

- Controls
  - PreTx: 0.8
  - PostTx: 0.6
  - $p = 0.02$

- Bone Marrow
  - PreTx: 0.8
  - PostTx: 0.2
  - $p = 0.02$
Effects of Fresh Autologous Bone Marrow Transplantation on LV Enddiastolic Volumes

- Controls
  - PreTx: 40 mL
  - PostTx: 55 mL
  - $p = 0.02$

- Bone Marrow
  - PreTx: 40 mL
  - PostTx: 58 mL
  - $p = 0.01$
Histology of Infarction

Control

Bone Marrow
Bone Marrow Transplantation

Purified Bone Marrow
(Hematopoietic progenitors/Stromal cells)

Advantage: Myocardial regeneration through differentiation into cardiomyocytes & endothelial cells

Results: Improved function & angiogenesis

Issues:

- Progenitors: selection of optimal cell population (CD34+, CD 133+) and scale-up
- Stromal cells: Poor clinical applicability of cardiomyogenic inducers (5-aza, co-cultures with CM)
Tx of CD133+ Hematopoietic Progenitors

Creation of MI in nude rats

Protocol

- Baseline echo assessment of LV function
- Transplantation of human cryopreserved myoblasts, CD133+ progenitors or culture medium
- Final echo assessment
- Explantation & Pathology

Day 0
8-10 Days
1 month
Phase I Clinical Studies of Bone Marrow Cell Transplantation

Protocol Outlines

- Adjunct-to-CABG surgical implantations (chronic MI) or adjunct-to-PTCA intracoronary injections (acute MI)

- Transplantation of freshly aspirated « whole » bone marrow (MNCs) or progenitors (CD133+)
Phase I Clinical Studies of Bone Marrow Cell Transplantation

Characteristics of Injected Cells

- Mononuclear cells
  - $9-28 \times 10^6$, $\approx 2\%$ CD34$^+$ (Strauer et al., Circulation 2002;106:1913-18)
  - $245 \times 10^6$, $\approx 3\%$ CD34$^+$ (Assmus et al., Circulation 2002;106:3009-17)

- Purified progenitors : CD133$^+$ (Stamm et al., Lancet 2003;361:45-6.)
Phase I Clinical Studies of Bone Marrow Cell Transplantation

Main Results

- Technical feasibility of the procedure
- Lack of adverse events
- Encouraging perfusion & function data which require validation by randomized trials
Pluripotency of mesenchymal stem cells derived from adult marrow


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§ Department of Microbiology, Center for Immunology, University of Minnesota Medical School, Minneapolis, Minnesota 55455, USA
¶ Department of Genetics, Cell Biology and Development, University of Minnesota Medical School, Minneapolis, Minnesota 55455, USA
† These authors contributed equally to this work
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Timing</th>
<th>Target area</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Early</td>
<td>Fresh infarct</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Myoblasts</td>
<td>Late</td>
<td>Fibrous scar</td>
<td>Myogenesis</td>
</tr>
</tbody>
</table>
Effects of Murine Embryonic Cardiomyocytes on Postinfarction Survival

Roell et al., Circulation 2002;105:2435-41
# Cell Transplantation

## Percutaneous Cell Transfer

<table>
<thead>
<tr>
<th>Approach</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoventricular</td>
<td>Electromagnetic</td>
</tr>
<tr>
<td>Transvenous</td>
<td>Echocardiographic</td>
</tr>
<tr>
<td>Intracoronary</td>
<td>Angiography</td>
</tr>
</tbody>
</table>
Transendocardial Delivery of Autologous Bone Marrow Enhances Collateral Perfusion and Regional Function in Pigs With Chronic Experimental Myocardial Ischemia

Shmuel Fuchs, MD,* Richard Baffour, PhD,* Yi Fu Zhou, MD,* Matte Shou, MD,* Anthony Petrie, BSc,* Fermin O. Tin, MD,† Neil J. Weissman, MD,* Martin B. Lenn, MD,‡ Stephen E. Epstein, MD,* Ran Kornowski, MD*

Washington, DC; San Antonio, Texas; and New York, New York

OBJECTIVES
We tested the hypothesis that intramyocardial injection of autologous bone marrow (ABM) promotes collateral development in ischemic porcine myocardium. We also defined, in vitro, whether bone marrow (BM) cells secrete vascular endothelial growth factor (VEGF) and macrophage chemotactic protein-1 (MCP-1).

BACKGROUND
The natural processes leading to collateral development are extremely complex, requiring multiple growth factors interacting in concert and in sequence. Because optimal angiogenesis may, therefore, require multiple angiogenic factors, we thought that injection of BM, which contains cells that secrete numerous angiogenic factors, might provide optimal therapeutic angiogenesis.

METHODS
Bone marrow was cultured four weeks in vitro. Conditioned medium was assayed for VEGF and MCP-1 and was added to cultured pig aortic endothelial cells (PAEC) to assess proliferation. Four weeks after left circumflex internal mammary implantation, heparinized ABM (n = 7) or heparinized saline (n = 7) was injected transendocardially into the ischemic zone (0.2 mL/injection at 12 sites). Echocardiography to assess myocardial thickening and microperfusion to assess perfusion were performed at rest and during stress.

RESULTS
Vascular endothelial growth factor and MCP-1 concentrations increased in a time-related manner. The conditioned medium enhanced, in a dose-related manner, PAEC proliferation. Collateral flow (ischemic/normal zone × 100) improved in ABM-treated pigs (ABM: 98 ± 14 vs. 33 ± 12 at rest, p = 0.003; 69 ± 18 vs. 78 ± 12 during adenosine, p = 0.025; controls: 92 ± 10 vs. 89 ± 9 at rest, p = 0.49; 78 ± 11 vs. 77 ± 13 during adenosine, p = 0.75). Similarly, contractility increased in ABM-treated pigs (ABM: 83 ± 21 vs. 60 ± 32 at rest, p = 0.4; 91 ± 44 vs. 36 ± 43 during pacing, p = 0.056; controls: 69 ± 48 vs. 64 ± 46 at rest, p = 0.74; 65 ± 56 vs. 37 ± 56 during pacing, p = 0.23).

CONCLUSIONS
Bone marrow cells secrete angiogenic factors that induce endothelial cell proliferation and, when injected transendocardially, augment collateral perfusion and myocardial function in ischemic myocardium. [J Am Coll Cardiol 2001;37:1726–32] © 2001 by the American
IVUS-Guided Transvenous Access
Percutaneous Transvenous Delivery of Skeletal Myoblasts
Intracoronary Infusion of Bone Marrow MNCs in Acute MI

Transplantation procedure

3-month perfusion data

Strauer et al. Circulation 2002;106:1913-18
Cell Transplantation

Catheter-Based Cell Delivery Techniques

- Technical feasibility of endoventricular, transvenous & intracoronary cell injections
- Limited data on cell retention & viability (≠ functionality)
- Unsettled issues:
  ✔ Functional comparisons with epicardial injections
  ✔ Transendothelial passage of intracoronarily injected cells
Early PostTransplant Myoblast Death Rate

% of β-gal loss

![Graph showing early posttransplant myoblast death rate with data points at h0 for beating heart (n=10), h0 for cardioplegically-arrested heart (n=4), h6 for beating heart (n=11), h24 for beating heart (n=9), h48 for cardioplegically-arrested heart (n=5), h72 for cardioplegically-arrested heart (n=3).]
Cell Transplantation

Mechanisms of Cell Death
- Physical strain related to injections
- Hypoxic environment
- Inflammatory reaction
- Apoptosis
## Patterns of Cell Death

<table>
<thead>
<tr>
<th>Environment</th>
<th>% of TUNEL-positive cells 1 day after Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cryoinjury</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>32.1 [0.01]</td>
</tr>
<tr>
<td>After heat shock prett</td>
<td>14.7 [0.05]</td>
</tr>
<tr>
<td>Vascularized granulation tissue</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Survival-Enhancing Strategies

- Induction of angiogenesis (preTx myoblast transfection or co-injections with angiogenic growth factors)
- Anti-apoptotic interventions (heat shock)
- Selection of a behaviorally distinct more resistant subpopulation of myoblasts
Myoblast Transplantation

Extension to Nonischemic Cardiomyopathies

- Encouraging results of fetal, smooth muscle and skeletal muscle cell Tx in small animal models of genetic and doxorubicin-induced cardiomyopathy
- Potential interest of catheter-based cell delivery techniques to achieve widespread cell distribution
1- Differences in membrane properties between engrafted myotubes and host cardiomyocytes might be the substrate of postTx ventricular arrhythmias.

2- Secretion of pleiotrophic factors could be one of the mechanisms whereby myoblast Tx improves LV function.

3- There is currently no evidence that bone marrow cells are superior to myoblasts when cell Tx is performed at the late stage of postMI scar.
Key Take-Home Messages : Clinical

1- Concerns about VTs should be tempered in view of a possible control by drugs and/or AICD
2- Percutaneous cell transfer might benefit from the transvenous approach
3- Encouraging efficacy data yielded by phase I human studies of autologous skeletal myoblast Tx need to be confirmed by randomized trials
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