NO REFLOW - THE ACHILLES HEEL OF REPERFUSION

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Reperfusion therapy has dramatically improved the outcome of patients with ST elevation MI.

Major limitations of reperfusion therapy are failure of epicardial reperfusion (more common with thrombolysis) and failure of tissue level reperfusion (“no reflow”).
FAILED TISSUE REPERFUSION - THE NO REFLOW PHENOMENON

A profound reduction in antegrade coronary blood flow in the absence of residual epicardial flow limitation or distal macroembolization.
NO REFLOW

- Mechanisms
- Prognosis
- Recognition
- Pharmacologic management
- Interventional management
Pathophysiology of microvascular dysfunction after epicardial perfusion in patients with acute myocardial infarction.
30-days Mortality & MACE

- Normal Flow
- No-Reflow

Mortality:
- Normal Flow: 3%
- No-Reflow: 10%

MACE:
- Normal Flow: 7.2%
- No-Reflow: 16%

P = 0.05
P = 0.09

Brosh et al. Am J Cardiol 2007;99:442
PREVALENCE & PREDICTORS OF NO REFLOW

• 232/3362 STEMI patients enrolled in the PAMI trials had TIMI ≤ 2 flow (6.9%).

• Predictors of TIMI ≤ 2 flow:
  – Age >70
  – Diabetes
  – Delayed reperfusion
  – Initial TIMI 0/1
  – LVEF <50%

Mehta et al. JACC 2003;42:1739
PREVALENCE & PREDICTORS OF NO REFLOW (2)

• 891 PPCI patients enrolled in GUSTO IIb & RAPPORT
• TIMI $< 2$ flow achieved in 19%

Cura et al. AJC 2001;88:124
NO REFLOW

- Increases with age
- Probably more common in LAD infarcts
- Largely reflects the extent of damage sustained PRIOR to reperfusion (time to treatment, LVEF, Q waves, occluded vessel prior to PCI). Whether reperfusion itself contributes to this damage remains controversial.
Can no reflow be predicted on admission?

• Predicting reperfusion success is important for selection of reperfusion modalities and ancillary therapies.

• Multiple investigators studied admission characteristics as predictors of epicardial recanalization but very few assessed the ability to predict myocardial reperfusion on admission.
Admission EKG analyzed only for Q waves
Grade of Ischemia

- Terminal QRS distortion (grade of ischemia [GOI]) reflects the severity of ischemia and is a strong independent prognostic factor in patients with STEMI.
Grade of Ischemia (Sklarovsky – Birnbaum)

- **Grade 1 (G1I)**
  - No ST elevation.

- **Grade 2 (G2I)**
  - ST-segment elevation which does not meet criteria for grade 3.

- **Grade 3 (G3I)**
  - Absence of S waves below the isoelectric line in leads that usually have a terminal S configuration (V1-V3).
  - ST J-point amplitude $\geq 50\%$ of the R-wave amplitude in other leads.
  - Grade 3 criteria in 2 adjacent leads required.
Grade of Ischemia

GRADE 2

GRADE 3

a
b
c
d

II  III  aVF

III

II  III  aVF
Grade of Ischemia

GRADE 2

GRADE 3
Features of Grade 3 Ischemia

- Larger infarct size in comparison to G2I patients despite a similar area at risk and independent of the success of epicardial reperfusion.
- Higher reinfarction rate.
- Higher mortality rate.
- The mechanism responsible for the worse prognosis associated with G3I is unknown.
GRADE 3 ISCHEMIA ON THE ADMISSION ELECTROCARDIOGRAM PREDICTS FAILURE OF ST RESOLUTION FOLLOWING THROMBOLYTIC THERAPY FOR ACUTE MYOCARDIAL INFARCTION

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Int J Cardiol 2005;104:131-7
CAN NO REFLOW BE PREDICTED ON ADMISSION?

• 180 patients with first anterior MI undergoing thrombolysis

• Multiple factors available on admission assessed as predictors of complete ST resolution @ 1, 2 & 24 h as a surrogate of no reflow

• Independent factors:
  – Grade 3 ischemia on admission
  – No prior use of beta blockers
  – Previous use of aspirin
Grades of ischemia and ST resolution following thrombolysis

% of patients with ST resolution

- **Grade 2 Ischemia**
  - 1h: 22%
  - 2h: 60%
  - 24h: 93%

- **Grade 3 Ischemia**
  - 1h: 5%
  - 2h: 19%
  - 24h: 51%

Significance levels:
- **P=0.04**
- **P<0.01**

Legend:
- Yellow: Grade 2 Ischemia
- Red: Grade 3 Ischemia
CONCLUSIONS

• Grade 3 ischemia is the strongest admission predictor of failure of ST resolution and of the need for rescue PCI in STEMI patients scheduled for thrombolysis.
Grade 3 Ischemia on the Admission Electrocardiogram Predicts Failure of ST Resolution and of Adequate Flow Restoration Following Primary Angioplasty for Acute Myocardial Infarction

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Department of Cardiology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva and Division of Cardiology, The University of Texas Medical Branch, Galveston, Texas, USA*

Am Heart J 2007;153:410
Objectives

• To determine whether failure of ST resolution following primary angioplasty can be predicted on admission

• To determine whether the adverse outcome associated with G3I is mediated through impaired tissue reperfusion.
Methods (1)

- A prospective observational study.
- Study population (N=100):
  - **Inclusion criteria:**
    - Consecutive patients admitted for a first STEMI and scheduled for PPCI.
  - **Exclusion criteria:**
    - >12h from symptoms onset.
    - LBBB
    - Paced or ventricular rhythm
    - Negative T waves in ≥2 adjacent leads with maximal ST elevation
    - Incomplete or uninterpretable ECG data.
Failure of STR vs. successful STR

- Pre infarction angina: 30% failure, 36% successful, ns
- Q waves: 18% failure, 10% successful, ns
- G3q: 42% failure, 16% successful, P<0.01
G3I vs. G2I

- **Q waves**
  - G3I: 22%
  - G2I: 11%
  - ns

- **STR≥70%**
  - G3I: 60%
  - G2I: 28%
  - P<0.01

- **STR≥50%**
  - G3I: 66%
  - G2I: 90%
  - P<0.01
G3I vs. G2I
angiographic results

- Initial TIMI grade 3 flow: G3I 7%, G2I 3%
- Initial TMP grade 3: G3I 14%, G2I 13%
- Final TIMI grade 3 flow: G3I 59%, G2I 92%
- Final TMP grade 3: G3I 22%, G2I 74%

ns p<0.01 ns P<0.01
Conclusions

• G3I is the strongest independent predictor available on admission of failure to achieve myocardial reperfusion as assessed both electrocardiographically and angiographically.

• Grade 3 ischemia probably reflects severe ischemic damage to the microvasculature.

• This observation may allow future investigators to identify on admission patients who are at high risk for failure of myocardial reperfusion.
Individual values of ET-1 plasma levels according to no-reflow occurrence

Plasma levels of thromboxane A2 on admission are associated with no-reflow after primary percutaneous coronary intervention

Giampaolo Niccoli, Simona Giubilato, Eleonora Russo, Cristina Spaziani, Andrea Leo, Italo Porto, Antonio M. Leone, Francesco Burzotta, Silvia Riondino, Fabio Pulcinelli, Luigi M. Biasucci, and Filippo Crea

Copyright restrictions may apply.
$P$ for trend $< 0.01$

- Lack of ST-segment resolution
- Angiographic no-reflow

Tertiles of TXA2 plasma levels (pg/mL)

CONCLUSIONS

• No reflow can be predicted on admission by:
  – High ET1 and, better, by high TXA2 levels
  – Grade 3 ischemia on the admission EKG

• The EKG is the most readily available tool for this purpose and therefore is probably the best method available at present for this purpose.
HOW CAN FULL REPERFUSION BE DETECTED?

• Bedside signs of reperfusion:
  – Resolution of symptoms
  – Rapid release of biomarkers
  – ST resolution
  – Reperfusion arrhythmias

• TIMI flow grade and CTFC
• Myocardial blush - TMPG
• Coronary Doppler wire
• Non invasive imaging: MRI, Contrast echo
Even Faster Epicardial Coronary Blood Flow is Better

- **Reproducibility:** 
  - $r = 0.97$ between readers
- **Accuracy:** 
  - $r = 0.88$ vs Doppler velocity

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Gibson, Circulation 1999; 99: 1945-1950

- **CTFC < 14**
  - 0.0% (n=41)
  - "TIMI 4" Flow
  - Hyperemic Flow

- **14 ≤ CTFC ≤ 40**
  - 2.8% (n = 18/640)
  - TIMI 3 Flow

- **CTFC > 40**
  - 6.2% (n = 35/563)

- **% Risk of In Hospital Mortality**
  - **p = 0.003**
TIMI Myocardial Perfusion (TMP) Grades

TMP Grade 3
- Normal ground glass appearance of blush
- Dye mildly persistent at end of washout
- p = 0.05
- Mortality: 2.0%
  - n = 203

TMP Grade 2
- Dye strongly persistent at end of washout
- Gone by next injection
- Mortality: 4.4%
  - n = 46

TMP Grade 1
- Stain present
- Blush persists on next injection
- Mortality: 5.1%
  - n = 79

TMP Grade 0
- No or minimal blush
- Mortality: 6.2%
  - n = 434

Gibson et al, Circulation 2000
Coronary Doppler wire

- Indicators of no reflow:
  - Systolic retrograde flow
  - Diminished systolic antegrade flow
  - Rapid deceleration of diastolic flow
<table>
<thead>
<tr>
<th></th>
<th>No Reflow</th>
<th>Reflow</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>40%</td>
<td>18%</td>
<td>0.005</td>
</tr>
<tr>
<td>CHF</td>
<td>21%</td>
<td>12%</td>
<td>0.001</td>
</tr>
<tr>
<td>In Hospital Death</td>
<td>6%</td>
<td>1%</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Tissue Level Perfusion by Myocardial Contrast ECHO & Outcomes


Ito et al, Circulation, 1996
Midventricular short-axis magnetic resonance image demonstrating acute transmural infarction of the lateral wall (arrowheads). A dense rim of subendocardial signal void (black arrow) corresponds to the region of no reflow or microvascular obstruction. Because gadolinium does not reach this portion of the myocardium, there is no T1 shortening. Therefore, no hyperenhancement can be visualized.
PHARMACOLOGICAL MANAGEMENT OF NO REFLOW

- ADENOSINE
- VERAPAMIL
- NITROPRUSSIDE
ADENOSINE:

- Promotes preservation of microvascular blood flow
- Inhibits neutrophils
- Restores key metabolic substrates
- Inhibits production of oxygen-derived free radicals
- Restores calcium homeostasis
- Mediates pre- and post-conditioning
AMISTAD II

2118 Patients
ASA

Placebo

Adenosine
50mcg/Kg/min
X 3h

Adenosine
70mcg/Kg/min
X 3h

Fibrinolysis or PTCA

Infarct size (≥5 d)
(243 patients)

Follow-up for 6 months

- Anterior Wall MI (STE, LBBB) ≤6h
- No contraindication for lysis
- No hypotension
- No bradycardia
- No obstructive airway disease
57% reduction in median infarct size with 70mcg/kg/min group relative to placebo
Effect of early reperfusion treatment (3.1 hrs) on clinical outcomes

- Placebo
- Pooled Adenosine

- * p=0.01
- **p=0.03
- + p=0.02
VERAPAMIL

- Relieves vessel spasm
- Improves calcium homeostasis in ischemic myocardial cells
- May inhibit platelet aggregation and thrombus formation in the microvasculature
- May reduce myocardial ischemia and infarct size by reducing heart rate and blood pressure
VERAPAMIL (2)

• Several small studies suggest that routine IC verapamil at the time of PCI prevents microvascular dysfunction and TIMI flow rates in STEMI and in SVG interventions
Nitroprusside

• A short acting potent vasodilator acting in the resistance arteriolar circulation
• Nitric oxide (NO) donor
• Intracoronary administration was found to be an effective and safe treatment for impaired blood flow and no-reflow during elective PCI [Hillegas at all. JACC-2001]
Intracoronary Nitroprusside for the Prevention of No-reflow Following Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction. A Randomized, Double Blind, Placebo-Controlled Clinical Trial.


Dept. of Cardiology,
Soroka University Medical Center & Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva

Am Heart J 2006;152:887.e9-14
Primary end point-
Corrected TIMI Frame Count

CTFC
Mean ± SEM

Control
NTP
P=0.78
Primary end point-
ST-segment elevation resolution

<table>
<thead>
<tr>
<th></th>
<th>NTP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>62 %</td>
<td>61 %</td>
</tr>
</tbody>
</table>

P = 0.96
NICORANDIL

- A hybrid of a K ATP opener and a nitrate
- Intravenous nicorandil, started before PPCI, improves tissue perfusion, reduces infarct size, and improves patient outcome (Ishii H Circulation 2005)
NICARDIPINE

- Highly potent microcirculatory vasodilator
- Longer duration of action
- Greater coronary vasoselectivity
- Minimal myocardial or AV nodal depression
Distal embolization of particles during primary PCI may be a major contributing cause of the suboptimal myocardial perfusion. Thus a device that could capture and remove thrombus or embolic particles before they reach the myocardium could improve myocardial perfusion.
The EMERALD Study
Infarct size by Tc-99m-SPECT
Infarct size, %LV

PercuSurge GuardWire in AMI
## Prevention of Distal Embolization in AMI: A Meta-Analysis TIMI 3 FLOW & MPG 3

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
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<tbody>
<tr>
<td><strong>DISTAL PROTECTION</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ASPARAGUS</td>
<td>127/165</td>
<td>128/164</td>
<td></td>
<td>11.20</td>
<td>0.94 [0.56, 1.58]</td>
</tr>
<tr>
<td>DIPLOMATIC</td>
<td>28/32</td>
<td>27/28</td>
<td></td>
<td>1.27</td>
<td>0.36 [0.04, 3.65]</td>
</tr>
<tr>
<td>EMERALD</td>
<td>219/239</td>
<td>215/241</td>
<td></td>
<td>9.63</td>
<td>1.32 [0.72, 2.44]</td>
</tr>
<tr>
<td>Nanasato et al.</td>
<td>34/34</td>
<td>28/30</td>
<td></td>
<td>0.75</td>
<td>6.05 [0.28, 131.25]</td>
</tr>
<tr>
<td>PREMIAR</td>
<td>52/66</td>
<td>50/70</td>
<td></td>
<td>7.31</td>
<td>1.49 [0.68, 3.26]</td>
</tr>
<tr>
<td>PROMISE</td>
<td>93/100</td>
<td>93/100</td>
<td></td>
<td>4.69</td>
<td>1.00 [0.34, 2.96]</td>
</tr>
<tr>
<td>Tahk et al</td>
<td>48/50</td>
<td>37/48</td>
<td></td>
<td>2.59</td>
<td>7.14 [1.49, 34.18]</td>
</tr>
<tr>
<td>UPFLOW</td>
<td>45/51</td>
<td>46/49</td>
<td></td>
<td>2.97</td>
<td>0.49 [0.12, 2.08]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>647/737</td>
<td>624/730</td>
<td></td>
<td>40.39</td>
<td>1.22 [0.79, 1.66]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 9.93 \), df = 7 \( P = 0.19 \), \( I^2 = 29.5\% \)

Test for overall effect: \( Z = 0.90 \) \( P = 0.37 \)

### Study

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<tr>
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<th>Weight %</th>
<th>OR (random) 95% CI</th>
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<tr>
<td>ASPARAGUS</td>
<td>42/167</td>
<td>32/158</td>
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<td>8.22</td>
<td>1.32 [0.78, 2.23]</td>
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<tr>
<td>DIPLOMATIC</td>
<td>9/32</td>
<td>0/28</td>
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<td>1.62</td>
<td>23.04 [1.27, 417.01]</td>
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<td>EMERALD</td>
<td>138/226</td>
<td>120/227</td>
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<td>8.81</td>
<td>1.40 [0.96, 2.03]</td>
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<td>Nanasato et al.</td>
<td>24/34</td>
<td>10/30</td>
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<td>5.77</td>
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<tr>
<td>PREMIAR</td>
<td>35/52</td>
<td>41/58</td>
<td></td>
<td>6.89</td>
<td>0.85 [0.38, 1.92]</td>
</tr>
<tr>
<td>Tahk et al</td>
<td>33/50</td>
<td>16/46</td>
<td></td>
<td>6.74</td>
<td>3.64 [1.57, 8.46]</td>
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<tr>
<td>UPFLOW</td>
<td>33/49</td>
<td>32/48</td>
<td></td>
<td>6.72</td>
<td>1.03 [0.44, 2.40]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>314/610</td>
<td>251/595</td>
<td></td>
<td>44.76</td>
<td>1.73 [1.09, 2.75]</td>
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</table>

Test for heterogeneity: \( \chi^2 = 15.34 \), df = 6 \( P = 0.02 \), \( I^2 = 60.9\% \)

Test for overall effect: \( Z = 2.32 \) \( P = 0.02 \)

De Luca G et al. AHJ 2007

Favours Control  Favours Adjunctive devices
Why did studies of distal protection in AMI PCI show no benefit?

- **Patient related issues?**
  - Distal protection may be beneficial in subgroups of patients (large size vessels with increased thrombotic load)

- **Device related issues?**
  - Crossing profile and wire manipulation
  - Sizing (especially small vessels)
  - Capturing (still sub-optimal in some cases)
  - Different device may be needed
  - Combination devices (i.e. sequential approach)

- **Misconception related issues?**
  - Myocardial preservation (i.e. pharmacologic) vs. mechanical protection approach or may be both
1071 STEMI patients randomized

535 were assigned to thrombus aspiration
- 33 did not undergo PCI
- 502 underwent primary PCI
  - 295 underwent TA followed by direct stenting
  - 153 underwent TA with additional balloon dilation
  - 54 had crossover to conventional PCI

530 complete follow-up at 1 year

536 were assigned to conventional PCI
- 33 did not undergo PCI
- 503 underwent primary PCI
  - 485 underwent balloon dilation followed by stenting
  - 12 underwent conventional PCI with additional TA
  - 6 had crossover to TA

530 complete follow-up at 1 year

Primary endpoint: Myocardial blush grade

Svilaas T et al. NEJM 2008;358:557 - FZ
2008-8
ST-segment elevation resolution

Patients (%)

- < 30%
- 30-70%
- > 70%

Thrombus aspiration

- < 30%
- 30-70%
- > 70%

Conventional PCI

P < 0.001

Svilaas T et al. NEJM 2008;358-557 - FZ
2008-9
TAPAS: Summary of findings at 30 days

- Thrombus aspiration results in improved myocardial reperfusion
- Myocardial blush grade predicts 30-day rates of death and reinfarction
- Does improved myocardial reperfusion translate into clinical benefit at 1 year?
Mortality at 1 Year


TAPAS: Mortality and reinfarction at 1 year

- Myocardial blush grade predicts clinical outcome at 1 year

- Thrombus aspiration results in a lower mortality and combined mortality and non-fatal reinfarction at 1 year
CONCLUSIONS

• No reflow is a common and serious complication of reperfusion therapy
• No reflow can be predicted by grade 3 ischemia, longer time to treatment and anterior MI
• Diagnosis based on TIMI flow and blush, failure of ST resolution
• No medical intervention consistently beneficial
• Thrombus aspiration is the best available strategy
THANK YOU!!!