Importance of Microvascular Obstruction on Images and Prognosis

Jan Bogaert
Radiology & Medical Imaging Research Centre

No Conflict of Interest
Myocardial protection: is primary PCI enough?

Derek J Hausenloy and Derek M Yellon

Adapted from Kloner and Jennings 2001

Timely and effective myocardial reperfusion using primary percutaneous coronary intervention (PCI) remains the most effective treatment strategy for limiting myocardial infarct size, reducing left ventricular remodeling, preserving left ventricular systolic function and improving clinical outcomes following a ST-segment elevation myocardial infarction (STEMI).

Consequences of ischemia/reperfusion
- Stunning (no necrosis)
- Preconditioning
- Tissue viability (no necrosis)
- Subendocardial necrosis (salvage of outer layers)
- Necrosis extends into midmyocardium, subepicardium
- Near transmural infarction (no salvage of tissue but may lead to negative LV remodeling)

Adapted from Kloner and Jennings 2001
The “No-Reflow” Phenomenon after Temporary Coronary Occlusion in the Dog

Robert A. Kloner, Charles E. Ganote and Robert B. Jennings

Department of Pathology, Northwestern University Medical School, Chicago, Illinois 60611

Published December, 1974

The role of microvascular damage in the genesis of the “no-reflow” phenomenon was investigated in the left ventricular myocardium of dogs subjected to temporary occlusions of a major coronary artery for 40 and 90 min. Intravenous carbon black or thioflavin S (a fluorescent vital stain for endothelium) were used to demonstrate the distribution of coronary arterial flow in control and damaged myocardium. These tracers were injected simultaneously with release of the coronary occlusion or after 5 or 20 min of reflow of coronary arterial blood. After 40 min of ischemia plus arterial reperfusion, usually the tracers were evenly distributed throughout the damaged tissue at each time of reperfusion. On the other hand, when

Published in Volume 54, Issue 6 (December, 1974)
Mechanisms responsible for No-Reflow

Figure 3: Mechanisms Responsible for No-Reflow

Four interacting mechanisms (distal embolization, ischemia-related injury, reperfusion-related injury, and individual susceptibility) contribute to microvascular injury and are responsible for no-reflow phenomenon. The contribution of these mechanisms to the pathogenesis of no-reflow is likely to vary in different patients.

Figure 5: Therapies of No-Reflow Targeted to Main Pathogenetic Mechanisms

A comprehensive figure showing multiple mechanisms involved in the pathogenesis of no-reflow that might be targeted by appropriate therapy. Figure illustration by Rob Fineall. ET - endothelin; TXA2 - thromboxane A2.
Figure 1  Time to Reperfusion and Cardiovascular Magnetic Resonance Parameters

Bar graphs show the influence of time to reperfusion on infarct size (A), myocardial edema (B), myocardial salvage (C), and microvascular obstruction (MVO) (D). Data are expressed as % left ventricular mass.
Ischemia Time – No-Reflow

Determinants and impact of microvascular obstruction in successfully reperfused ST-segment elevation myocardial infarction. Assessment by magnetic resonance imaging

Table 5 Relationship between infarct size, presence or absence of MVO, and the degree of MVO transmurality

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*Infarct size normalized to LV mass
Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction

Javier Ganame, Giancarlo Messalli, Steven Dymarkowski, Frank E. Rademakers, Walter Desmet, Frans Van de Werf, and Jan Bogaert

Myocardial haemorrhage, the presence of which can easily be detected with T2-weighted MRI, is a frequent complication after successful myocardial reperfusion and an independent predictor of adverse LV remodelling regardless of the initial infarct size.
Conclusions—A hypointense infarct core within the area at risk of reperfused infarcted myocardium in T2-weighted CMR is closely related to infarct size, microvascular obstruction, and impaired left ventricular function, with subsequent adverse clinical outcome. (Circ Cardiovasc Imaging. 2011;4:354-362.)

Figure 5. Unadjusted survival curves of the cumulative incidence of death, reinfarction, and new congestive heart failure during the first 6 months after infarction in patients with and without the presence of a hypointense core in T2-weighted imaging (A) and in patients with hypointense core and MO both present (IMH), MO only present, and patients with neither MO nor hypointense core (B).
Thrombus Aspiration During Primary Percutaneous Coronary Intervention Improves Myocardial Reperfusion and Reduces Infarct Size

The EXPIRA (Thrombectomy With Export Catheter in Infarct–Related Artery During Primary Percutaneous Coronary Intervention) Prospective, Randomized Trial

<table>
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<th>Table 4: Cardiac Magnetic Resonance Imaging Results</th>
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<th>Acute Phase</th>
<th>3-Month Follow-Up</th>
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<tr>
<td></td>
<td>S-PCI (n = 37)</td>
<td>EM-PCI (n = 38)</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>137.5 ± 18.6</td>
<td>131.5 ± 14.4</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>77.4 ± 15.4</td>
<td>71.3 ± 17.3</td>
</tr>
<tr>
<td>EF, %</td>
<td>44.3 ± 9.5</td>
<td>46.3 ± 8.6*</td>
</tr>
<tr>
<td>IS, %</td>
<td>13 ± 6.7</td>
<td>14 ± 12†</td>
</tr>
<tr>
<td>IS, g</td>
<td>14 ± 7.5</td>
<td>17 ± 15‡</td>
</tr>
<tr>
<td>MVO, n</td>
<td>27 (72.9%)</td>
<td>9 (31.5%)</td>
</tr>
<tr>
<td>MVO, g</td>
<td>3.7 ± 2.6</td>
<td>1.7 ± 1.9</td>
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Results

Myocardial blush grade ≥2 and ST-segment resolution occurred more frequently in the EM-PCI group (88% vs. 60%, p = 0.001; and 64% vs. 30%, p = 0.001). In the acute phase, microvascular obstruction extent was significantly lower in the EM-PCI group and at 3 months, infarct size was significantly reduced only in the EM-PCI group. A lower incidence of cardiac death in the EM-PCI group (4.6% vs. 0%, log-rank test p = 0.02) was observed at 9 months.

Conclusions

Thrombectomy prevents thrombus embolization and preserves microvascular integrity reducing infarct size, and it therefore represents an useful adjunctive therapy in PCI. (J Am Coll Cardiol 2009;53:309–15) © 2009 by the American College of Cardiology Foundation.
Diagnosis of No-Reflow

- Coronary angiography (TIMI flow grade – Myocardial Blush Grade)
- ECG (STR 1h after PPCI)
- Myocardial contrast echocardiography (MCE)
- Cardiac MRI

Figures 4, 5. (4) Pre- (a) and postcontrast (b) images through left ventricle of patient with anterior wall infarction. Note subendocardial enhancement with patchy areas of low signal intensity adjacent to the enhancing infarct (type 3 pattern). R = right. (5) Pre- (a) and postcontrast (b) images through left ventricle of patient with nonreperfused infarct posterolaterally illustrate the doughnut pattern of enhancement (type 4).
Prognostic Significance of Microvascular Obstruction by Magnetic Resonance Imaging in Patients With Acute Myocardial Infarction
Katherine C. Wu, Elias A. Zerhouni, Robert M. Judd, Carlos H. Lugo-Olivieri, Lili A. Barouch, Steven P. Schulman, Roger S. Blumenthal and João A. C. Lima
Circulation 1998;97:765-772

Conclusions—After infarction, MRI-determined microvascular obstruction predicts more frequent cardiovascular complications. In addition, infarct size determined by MRI also relates directly to long-term prognosis in patients with acute myocardial infarction. Moreover, microvascular status remains a strong prognostic marker even after control for infarct size. (Circulation. 1998;97:765-772.)
• Morphology  (T1w-SE MRI / cine MRI)
• Myocardial edema (T2w-STIR-SE MRI)
• Cardiac function
  – Systolic (cine MRI / tagging)
  – Diastolic function: (VENC cine MRI)
• Myocardial perfusion imaging (MPI)
• Tissue Characterization
  – late or delayed (gadolinium) enhancement
  – T2* sequences
• Flow & Motion imaging
  – b-SSFP cine MRI
  – velocity-encoded cine MRI
• Vessel (coronary artery imaging)
  – b-SSFP 3D MR(C)A
  – contrast-enhanced 3D MR(C)A
CMR depiction of No-Reflow
Functional Recovery After Acute Myocardial Infarction
Comparison Between Angiography, Electrocardiography, and Cardiovascular Magnetic Resonance Measures of Microvascular Injury

Robin Nijveldt, MD,*§ Aernout M. Beek, MD,* Alexander Hirsch, MD,§ Martin G. Stoel, MD,† Mark B. M. Hofman, PhD,† Victor A. W. M. Umans, MD, PhD,# Paul R. Algra, MD, PhD,** Jos W. R. Twisk, PhD,‡ Albert C. van Rossum, MD, PhD*§ J Am Coll Cardiol 2008;52:181-189

In patients after revascularized AMI, late MVO proved a more powerful predictor of global and regional functional recovery than all of the other characteristics, including transmural extent of infarction. (J Am Coll Cardiol 2008;52:181-9) © 2008 by the American College of Cardiology Foundation

Impact of early vs. late microvascular obstruction assessed by magnetic resonance imaging on long-term outcome after ST-elevation myocardial infarction: a comparison with traditional prognostic markers


In contrast to early MO, the presence and extent of late MO are strong independent prognosticators after STEMI. www.ClinicalTrials.gov. NCT00299377.
Microvascular Obstruction

- MVO is frequently present in both STEMI (>50%) and non-STEMI infarcts

- increases with the duration of ischemia time (Tarantini et al. 2005; Francone et al. 2009)

- is related to more severe myocardial damage (Bogaert et al. 2007)

- ….. together with other parameters such as intramyocardial hemorrhage (Ganame et al. 2009; Mather et al. 2010)

- dynamic phenomenon over time (Rochitte et al. 1998; Reffelmann et al. 2003)

High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction

Walter Desmet mápawn, Jan Bogaert, Christophe Dubois, Peter Sinnaeve, Tom Adriaenssens, Christos Pappas, Javier Ganame, Steven Dymarkowski, Stefan Janssens, Ann Belmans, and Frans Van de Werf

We found no evidence that selective high-dose intracoronary administration of adenosine distal to the occlusion site of the culprit lesion in STEMI patients results in incremental myocardial salvage or a decrease in microvascular obstruction.

Clinical Trial Registration Information: ClinicalTrials.gov number, NCT00284323.

Nitric Oxide Inhalation Improves Microvascular Flow and Decreases Infarction Size After Myocardial Ischemia and Reperfusion

Xiaoshun Liu, MD, PhD,* Yanming Huang, MD, PhD,* Peter Pokrcisz, PhD,† Pieter Vermeersch, MD,† Glenn Marsboom, MSC,† Marc Swinnen,* Eric Verbeken, MD, PhD,‡ Jose Santos, MD,* Marijke Pellens,† Hilde Gillijns,† Frans Van de Werf, MD, PhD,* Kenneth D. Bloch, MD,§ Stefan Janssens, MD, PhD*†

Leuven, Belgium; and Boston, Massachusetts

Inhalation of NO just before and during coronary reperfusion significantly improves microvascular perfusion, reduces infarct size, and may offer an attractive and novel treatment of myocardial infarction. (J Am Coll Cardiol 2007;50:808–17) © 2007 by the American College of Cardiology Foundation
Conclusions

• shift from ‘open coronary artery’ toward ‘open microvessel’ therapies in AMI patients

• combination of edema / contrast-enhanced MRI probably the best to characterize the infarcted myocardium
  – area-at-risk / myocardial salvage / myocardial hemorrhage
  – myocardial infarct size / transmurality
  – no-reflow / microvascular obstruction (‘free bonus of CMR infarct imaging’)

• unresolved issues are exact timing post PCI - post contrast administration

• novel strategies are targeted toward reduction of microvascular damage
Timely and effective myocardial reperfusion using primary percutaneous coronary intervention (PCI) remains the most effective treatment strategy for limiting myocardial infarct size, reducing left ventricular remodeling, preserving left ventricular systolic function and improving clinical outcomes following a ST-segment elevation myocardial infarction (STEMI).

The existence of no-reflow phenomenon was initially debated; however, a large amount of experimental and clinical data have clearly shown that it occurs after reperfusion with a variable prevalence, ranging from 5% up to 50%, according to the methods used to assess the phenomenon and to the population under study (2,3).
Reperfused and Nonreperfused Myocardial Infarction: Diagnostic Potential of Gd-DTPA–enhanced MR Imaging

Radiology 1989; 172:717–720

Figures 4, 5. (4) Pre-(a) and postcontrast (b) images through left ventricle of patient with anterior wall infarction. Note subendocardial enhancement with patchy areas of low signal intensity adjacent to the enhancing infarct (type 3 pattern). R = right. (5) Pre-(a) and postcontrast (b) images through left ventricle of patient with nonreperfused infarct posterolaterally illustrate the doughnut pattern of enhancement (type 4).
• extensive infarct with low EF LV (28%)
• day 3 post-infarct
Detection of Acutely Impaired Microvascular Reperfusion After Infarct Angioplasty With Magnetic Resonance Imaging

Andrew J. Taylor, PhD; Nidal Al-Saadi, MD; Hassan Abdel-Aty, MD; Jeanette Schulz-Menger, MD; Daniel R. Messroghi, MD; Matthias G. Friedrich, MD

Conclusions—CMR detects impaired microvascular reperfusion in AMI patients despite successful infarct angioplasty, which when severe is associated with a lack of recovery of wall motion. (Circulation. 2004;109:2080-2085.)

Determinants and impact of microvascular obstruction in successfully reperfused ST-segment elevation myocardial infarction. Assessment by magnetic resonance imaging.

On early (i.e., 2–5 min) post-contrast MRI, MVO was detected in 32 patients with an MVO to infarct ratio of 36.3 ± 24.9%. On late (i.e., 10–25 min) post-contrast MRI, MVO was detected in only 27 patients, with an MVO to infarct ratio of 15.9 ± 13.9%.
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Andrew J. Taylor, PhD; Nidal Al-Saadi, MD; Hassan Abdel-Aty, MD; Jeanette Schulz-Menger, MD; Daniel R. Messroghli, MD; Matthias G. Friedrich, MD

Conclusions—CMR detects impaired microvascular reperfusion in AMI patients despite successful infarct angioplasty, which when severe is associated with a lack of recovery of wall motion. (Circulation. 2004;109:2060-2065.)
Appearance of microvascular obstruction on high resolution first-pass perfusion, early and late gadolinium enhancement CMR in patients with acute myocardial infarction

Adam N Mather¹, Timothy Lockie²,³, Eike Nagel³, Michael Marber², Divaka Perera², Simon Redwood², Aleksandra Radjenovic⁴, Ansuman Saha¹, John P Greenwood¹ and Sven Plein*¹,³

* Corresponding author. Email: sven.plein@uzleuven.be

Journal of Cardiovascular Magnetic Resonance 2009, 11:33
first pass perfusion

DE MRI

DE MRI 1Y FU
Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial

Stefan Janssens, Christophe Dubois, Jan Bogaert, Koen Theunissen, Christophe Deroose, Walter Desmet, Maria Kalantzi, Lieven Herbots, Peter Sinnaeve, Joseph Dens, Johan Maertens, Frank Rademakers, Steven Dymarkowski, Olivier Gheysens, Johan Van Cleemput, Guy Bormans, Johan Nuyts, Ann Belmans, Luc Mortelmans, Marc Boogaerts, Frans Van de Werf

Cell transfer did not greatly increase LV ejection fraction, refuting our primary hypothesis that in timely reperfused myocardial infarction BMSC transfer would significantly augment functional recovery. Although subgroup analysis should be considered cautiously in view of the size and exploratory nature of our study, lack of treatment effect on global functional recovery was not affected by infarct size, transmurality, or time from symptom onset to reperfusion.

Finally, microvascular obstruction occurred irrespective of treatment assignment in more than half of patients, despite restored epicardial coronary flow and normalised corrected TIMI frame counts. Its importance in hindering functional recovery and predicting outcome has been recognised.\textsuperscript{12,13} Although our study was not powered to examine the interaction of this complication with cell transfer, both the increase in LV ejection fraction and reduction in infarct size were greatly enhanced after cell transfer in patients without microvascular obstruction, suggesting an important target for future clinical investigation.
Imaging in Ischemic Heart Disease

- **CA anatomy** (stenosis detection/exclusion)
- **CTCA / MRCA**
- **“functionality”** (inducible ischemia)
- **stress perfusion**
- **stress function**
- **consequences of CA disease**
- **infarct/viability**
Determinants and impact of microvascular obstruction in successfully reperfused ST-segment elevation myocardial infarction.

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*Infarct size normalized to LV mass

![Infarct MRI](image)

Fig. 5: Tl-ratio in the MVO area between the early- and late post-contrast MRI in a patient with an extensive infarction of the anteroseptal LV wall. a Early post-contrast MRI shows extensive dark area (arrows). b Late post-contrast MRI shows partial fill-in of the MVO area with a remaining, mainly subendocardially located hypo-intense area (arrows). c Follow-up study at 4 months shows important thinning of the infarcted area (arrows). Notice the presence of the remaining rim of viable subepicardial tissue.
Value of T2-Weighted Magnetic Resonance Imaging Early After Myocardial Infarction in Dogs: Comparison With Bis-Gadolinium-Mesoporphyrin Enhanced T1-Weighted Magnetic Resonance Imaging and Functional Data From Cine Magnetic Resonance Imaging

Dymarkowski, Steven MD; Ni, Yicheng MD, PhD; Miao, Yi MD, PhD; Bogaert, Jan MD, PhD; Rademakers, Frank MD, PhD; Bosmans, Hilde PhD; Marchal, Guy MD, PhD

Rationale and objectives. Magnetic Resonance Imaging (MRI) has proved to provide noninvasive methods to investigate the functional repercussion of myocardial infarction and to measure infarct size with specific contrast agents. In this study, we evaluate whether the combination of T2-weighted and contrast-enhanced T1-weighted MRI could detect and discern necrotic and ischemic, but salvageable, myocardium.

Conclusion. In this study, the difference between the hyperintense areas on T2-weighted and enhanced T1-weighted images after myocardial infarction likely represents viable myocardium.

Investigative Radiology: February 2002 - Volume 37 - Issue 2 - pp 77-85

Analysis of myocardial oedema by magnetic

Edema as a Very Early Marker for Acute Myocardial Ischemia

A Cardiovascular Magnetic Resonance Study

Hassan Abdel-Aty, MD,* Myra Cocker, BSc,* Cheryl Meek, RN;† John V. Tyberg, MD, PhD;† Matthias G. Friedrich, MD*

Quantification of Myocardial Area at Risk With T2-Weighted CMR

Comparison With Contrast-Enhanced CMR and Coronary Angiography

Jeremy Wright, MBBS,*‡ Tom Adriaenssens, MD,† Steven Dymarkowski, MD, PhD,* Walter Desmet, MD, PhD,† Jan Bogaert, MD, PhD*

Cardiovascular Research 1993:27:1462-1469

EDITIONAL COMMENT

Myocardial Edema Imaging of the Area at Risk in Acute Myocardial Infarction

Seeing Through Water*

Hassan Abdel-Aty, MD
Contrast-Enhanced Inversion Recovery MRI

- \( Mz \)
- \( Mxy \)
- \( \alpha \)
- TI or inversion time

**null point (tissue specific)**

**normal myocardium**

**scarred myocardium**

- Delayed (Contrast) Enhancement (DE / DCE) MRI
- Late (Gadolinium) Enhancement (LE/LGE) MRI

Simonetti et al. Radiology 2001