The influence of myocardial edema on microvascular obstruction during ST-elevation myocardial infarction

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DISCLOSURES

DSMB / CEC – Abbott Vascular, BioVentrix, AltaValve

Speaker / Research – TherOx / Zoll, Boehringer-Ingelholm

Intraluminal and Extravascular Factors of Microvascular Injury Before, During and After Reperfusion that result in MVO

Sezar et al. JAHA 2018
Contribution of Lethal Reperfusion Injury Contributes up to 40% of Final Infarct Size


89 y/o female with 20 hours of SOB and chest and shoulder tightness
Pre- and Post-Coronary Angiogram

- Observed on cMRI in 40-70% of STEMI patients.
- Manifested as persistent ST-elevation on EKG or as No-Reflow following PCI.
- Likely diverse etiologies including:
  - Distal athero-embolic debris and platelet and WBC clumping
  - Microvascular dysfunction secondary to I/R injury.
  - Extrinsic compression of micro-vessels due to edema.
  - Destruction of vascular integrity and intramyocardial hemorrhage (IMH).
MVO is represented by hypo-enhanced (orange) region inside the hyper-enhanced (yellow) infarct region

1025 STEMI Patients who received primary PCI.

Freedom from cardiac death CHF, recurrent MI.

MVO more powerful predictor than Infarct size

Increasing amounts of MVO are Associated with Increased All-cause Mortality and Heart Failure Admissions over 1-Year

Data pooled from 7 Randomized Primary PCI Trials where MVO was Measured by cMRI Within 7 days of STEMI. MVO occurred in 57% of All Patients
What is the Long-Term Cardiac MRI Data of Patients with MVO Following STEMI?

The NHLBI TIME Trial:  
Role of Microvascular Obstruction in 2-Year Clinical and MRI Follow-up

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Principal Investigator, TIME Study  
Minneapolis Heart Institute at Abbott Northwestern Hospital  
University of Minnesota Medical School  
Cardiovascular Cell Therapy Research Network (CCTRN)

2016 Scientific Sessions of the AHA
Change in LV Ejection Fraction (%) over 2 Years

- **BMC**
- **Placebo**

Baseline Data Stratified by MVO

<table>
<thead>
<tr>
<th></th>
<th>MVO (n=47)</th>
<th>No MVO (n=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>55.2</td>
<td>58.3</td>
<td>0.120</td>
</tr>
<tr>
<td>Female (n)</td>
<td>1/15</td>
<td>14/15</td>
<td>0.001</td>
</tr>
<tr>
<td>Infarct Size (g)</td>
<td>52.8</td>
<td>34.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak CK (IU/ml)</td>
<td>3925</td>
<td>2439</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>43.1</td>
<td>46.6</td>
<td>0.078</td>
</tr>
<tr>
<td>LVEDVI (ml/m2)</td>
<td>80.2</td>
<td>71.1</td>
<td>0.006</td>
</tr>
<tr>
<td>LVESVI (ml/m2)</td>
<td>46.0</td>
<td>38.4</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Effect of MVO on Changes in LVEF and Volumes at 6-months


- Patients with MVO who received BMCs had a significant improvement in LV function and less adverse remodeling compared to patients with MVO who received placebo.
MVO (no-Reflow) – Historical Perspectives

- First identified in the Brain -> 2.5 minute occlusion of cerebral vessel resulted in impaired blood flow
- Kloner et al. (JCI 1974) – “The no-reflow phenomenon after temporary coronary occlusion in the dog”.
  - 40 minutes ischemia – normal reperfusion
  - 90 minutes ischemia – only partial restoration of blood flow.
  - **Histology** – significant capillary damage, endothelial cell swelling and protrusions
  - Less common were fibrin and platelet thrombi
  - Prominent interstitial and myocardial edema compressing capillaries

MVO (no-Reflow) – Historical Perspectives

- More pronounced in the subendocardium
- Increases with ischemic duration
- It is a “process” rather than an immediate “event” (unlike distal embolization in bypass graft PCI).
- No reflow area increases with time.
Ischemia-Reperfusion Injury – The nexus between myocardial edema and MVO

Water movement across cell membranes is passive and determined by osmotic gradients and membrane permeability to water. Myocardial water content is around 79 g per 100 g of cardiac tissue.

At the beginning of reperfusion the intravascular space is suddenly occupied by blood with physiologic osmolarity and tonicity as well as normal values of Na+, Cl-, proteins. Then, an osmotic gradient between the intravascular and interstitial spaces develops and water moves from the vascular space to the interstitium.

Endothelial damage increases not only water permeability but also protein leakage thus enhancing interstitial edema.

Differentiation of intra- from extracellular water remains a largely unmet challenge. There are not MRI applications to differentiate water distribution in the heart.
Development of Myocardial Edema is Dependent on Reperfusion

- 21 pigs subjected to LAD occlusion and reperfusion after 48 mins (n=7) or 78 mins (n=7) of ischemia or no reperfusion (n=6).
- Excised hearts underwent cMRI for T2 measurements
- Measurement of actual water content in myocardium performed

| Ischemia- Reperfusion Injury Manifests as Myocardial and Interstitial Edema |

![Graph showing ischemic and remote zones with end-diastolic wall thickness over time during ischemia and reperfusion](image)

Turschner O, et al. EHJ 2004
Conclusion: In STEMI patients, LYH is associated with more pronounced structural and functional alterations in CMR imaging as an indicator for adverse clinical outcomes in STEMI survivors.

Conclusions: Patients with LVH undergoing STEMI have larger infarct size underestimated by the LV systolic performance in comparison to patients without LVH.

TIME COURSE of MVO, Edema, IMH and INFARCT SIZE

- 10 pigs underwent 90-min coronary occlusion followed by reperfusion.
- Cardiac MRIs performed at Day-2, Week-1, 2, 4, 6

The MRI relaxation times T1, T2, and T2* are affected in different ways with respect to their sensitivity to the presence of edema or hemorrhage within the tissue matrix.

T2 appears to be a reliable indicator of inflammation post-AMI however, edema and hemorrhage have counter-acting effects on T2, and hence care should be taken while evaluating day 2.

At day 2, edema-related T2 elevation in the infarct zone was blunted by hemorrhagic by-products that could be identified by T2* signal voids; (2) at week 2, T2* reduction in the infarct zone was associated with hemorrhage as well as mineralization (calcium).


TIME-COURSE of MYOCARDIAL EDEMA in HUMANS FOLLOWING STEMI

Dall'Armellina et al. Circ Cardiovasc Img 2011

Carick D, et al. JAHA 2016
**Change in LV mass and Infarct Size over 2 Years**

<table>
<thead>
<tr>
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<th>LV Mass (g)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMC</td>
</tr>
<tr>
<td>Baseline</td>
<td>56</td>
</tr>
<tr>
<td>6 month</td>
<td>56</td>
</tr>
<tr>
<td>1 year</td>
<td>56</td>
</tr>
<tr>
<td>2 years</td>
<td>56</td>
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Traverse JH et al. Circ Res 2018

- We hypothesized that increased extravascular compressive forces in the myocardium that arise from the development of myocardial edema because of ischemia-reperfusion injury would contribute to the development of MVO.

- We measured MVO, infarct size, and left ventricular mass in patients with STEMI (n = 385) using cardiac MRI 2 to 3 days following successful percutaneous coronary intervention and stenting.

- MVO was found in 57% of patients with STEMI.
**Increased Extravascular Compressive Forces Contribute to MVO**

- Coronary Vasculature is embedded in the myocardium resulting in compression in systole such that the majority of coronary perfusion occurs in diastole.

- Even in diastole there is compression of the microvasculature that is dependent on the left-ventricular diastolic pressure (LVEDP).

- Increased wall stress associated with increased myocardial mass (LVH).

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- Patients with MVO had significantly greater infarct size and reduced left ventricular (LV) function ($P < 0.01$) compared with patients without MVO.

- MVO mass increases linearly with infarct size ($P < 0.001$).

Bonfig N, et al. AJP 2022
**MVO Mass Increases Linearly with LV Mass and is associated with Greater Myocardial Edema**

*Figure 3.* Plot of microvascular obstruction (MVO) mass vs. left ventricular (LV) mass (n = 167) as measured by cardiac MRI demonstrating that MVO mass increased with increasing LV mass, P < 0.001.

*Figure 4.* Plot of myocardial edema vs. left ventricular (LV) mass index (g/m²) in a subgroup of patients that underwent T2 imaging demonstrating a strong correlation of increasing myocardial edema with increasing LV mass index (n = 63).

*Figure 5.* Myocardial edema (area at risk [AAR]) in patients with (n = 39) and without (n = 24) microvascular obstruction (MVO). AAR was significantly greater in those patients who had MVO compared with those without MVO. Data are expressed as means ± SD, P < 0.01.

**Table 2.** Higher LVEDP is associated with the presence of MVO

<table>
<thead>
<tr>
<th></th>
<th>MVO</th>
<th>No MVO</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>20 ± 8</td>
<td>23 ± 8</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of patients; LVEDP, left ventricular end-diastolic pressure; MVO, microvascular obstruction.

Bonfig N, et al. AJP 2022
Measurement of zero-flow pressure ($P_{zf}$) in maximally-dilated dog heart (adenosine) under normal and elevated LVEDP (CHF) as surrogate for Extravascular Compressive Forces

Why doesn’t everyone get MVO post-STEMI?

- On average, 40-60% of STEMI patients get MVO.
- MVO tends to increase with infarct size and ischemic duration.
- Our initial data from TIME trial suggested that maybe females have less MVO than men.
- Other Unknown Factors ??
A Circadian Basis for Onset of Myocardial Infarction, Tolerance to Ischemia and MVO

In their original clinical descriptions of acute myocardial infarction in 1910, Oberstudt and Struthers noted, "Direct events often precipitated the disease; the infarct began in one case on climbing a high staircase, in another during an unpleasant conversation, and in a third during emotional distress associated with a heated card game." Their view, that infarction was triggered, was challenged in the 1980s as larger studies revealed that myocardial infarction often occurred without an obvious precipitating event. Authors argued for and against the belief that triggers were frequent. The controversy was eventually suspended for many years at Muster's conclusion, based on retrospective epidemiology, that "coronary occlusion takes place irrespective of the physical activity being performed or the time of onset" gained widespread acceptance. However, studies conducted with modern epidemiological methods and with new understanding of the pathogenesis of myocardial infarction indicate that the original concept of Oberstudt and Mintzer remains critical for clarifying the role of potential triggers.

Epidemiological evidence that morning anti-fines trigger onset

Myocardial infarction does not occur randomly throughout the day, but shows prominent circadian variation with increased morning frequency, supporting the concept that daily activities are important triggers. Evidence obtained from the MELIS study (1) and from the InternationalMainMenu study (2) clearly show that myocardial infarction is at least in part circadian.

Cohen, Muller

PHYSIOLOGIC REASONS FOR THE MORNING INCREASE IN CARDIOVASCULAR EVENTS: ACUTE RISK FACTORS

The key pathophysiological process underlying (CD, MI, and stroke due to thrombosis) the rupture of vulnerable atherosclerotic plaques. Such disruption exposes internal collagen and tissue factor, which in turn serve as a factor for platelet aggregation and resultant thrombus formation. Vulnerable atherosclerotic plaque has a rich lipid core and thin fibrous cap; the strength of the cap is derived from collagen and elastin produced by smooth muscle cells. These proteins are degraded by proteases produced by macrophages, which develop into foam cells. This degradation of collagen and elastin and platelet aggregation (e.g., fig 3) lead to the formation of a thrombus.

This increase in platelet recruitment is also due to the role of participation in adhesion. Antiplates tend to increase coronary vasoconstriction, possibly.
June 11, 1987
DOI: 10.1056/NEJM198706113162405

PLATELET AGGREGATION

EPI- / NOREPINEPHRINE

Lefer DJ Circ Res 2010;106:430
Circ Res 2012;110:105-110

39

20 of 31

20 of 31

39

40

20 of 31
For a given ischemic duration, myocardial injury was greatest with coronary occlusion onset around 1 AM or reperfusion around 4 AM.


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Circadian dependence of microvascular obstruction during ST-segment elevation myocardial infarction

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Bonfig et al. Int J Cardiol 2022

Bonfig et al. Int J Cardiol 2022
“Out of this World” Revelations About Infarct Size Following STEMI!

Prevailing Dogma about Infarct Size

“The infarct is largely completed after 6 hours of ischemia”? 

Intracoronary aqueous oxygen perfusion, performed 24 h after the onset of Post-infarction reperfusion, experimentally reduces infarct size and improves left ventricular function

J. Richard Spears,*, Petar Prcevski, Alice Jiang, Giles J. Brereton, Richard Vander Heide. Department of Medicine, Division of Cardiology, Wayne State University School of Medicine, Detroit, MI, United States

RESULTS

Late Presenters (12-24 hrs.) at higher risk of cardiac complications, heart failure, shock

COVID Era – Late presenters had increased mechanical complications

Multiple studies show benefit of PCI in late-presenters if ongoing ischemia
  - FAST-MI – 1169 pts presented 12-48 hrs. compared to 5104 early STEMI presenters – PCI reduced mortality
  - Polish Registry – 44% of 2036 Late presenters (12-24 hrs.) had PCI – Lower mortality at 12 mo. (9.3 vs. 17.9%).
  - BRAVE-2 – 365 STEMI pts (12-48 hrs.) randomized to PCI vs Conservative Tx. PCI group had smaller infarct size (8 vs 13%) and Lower MACE at 30 days (4.4 vs 6.6%).
  - No studies to date have explored if the addition to SSO2 to PCI in Late-Presenters will improve outcomes and LV function

MRI Analysis of our SSO2 Patients at MHI

- 11 patients with late-presentation Anterior STEMIs, most already had q-waves in the anterior leads
  - 6 Male, 5 Female. Age = 61 ± 8 years
  - Ischemic time = 14 ± 7 hours
  - TIMI Pre: 0 = 9; 1 = 2
  - TIMI Post: 3 = 9; 2 = 1; 1 = 1
  - LVEF = 40.6 ± 6.8 %
  - Infarct Size = 28 ± 5 % of LV
  - MVO = 5 = Yes; 4 = No

- All patients remain alive, 1 patient received ECMO followed by LVAD
LVEF Follow-up

- LVEF improved from 42 ± 10 to 56 ± 9 % by echocardiography at a mean of 76 days post-PCI (P < 0.05).

What’s Worse than MVO?
Intramyocardial Hemorrhage (IMH) Following STEMI

- May occur in up to 50% of STEMI patients as consequence of reperfusion injury.
- Associated with severe microvascular injury leading to loss of microvascular integrity and extravasation of blood into intramyocardial space.
- Breakdown products of RBC including iron are toxic to myocardium, increasing inflammation and contributes to infarct expansion.

Troponin kinetics and Infarct size in STEMI patients with (n=45) and without IMH (n=19) following PCI.
Canines with and without IMH have similar infarct size relative to AAR at one hour post-reperfusion of 3-hr LAD coronary occlusion.

By 24 hours, IS dramatically increases in dogs with IMH but not in dogs without IMH and loss of myocardial salvage potential. “Infarct Surge”

Enigma! It is not known why some dogs had IMH and other dogs (humans) do not.

MVO (and IMH) Remain the most important Remaining Targets in STEMI!

- Currently there are no therapeutic options to Reduce MVO!
- Need an MVO Manhattan Project!

Optimized Treatment of ST-Elevation Myocardial Infarction

The Unmet Need to Target Coronary Microvascular Obstruction as Primary Treatment Goal to Further Improve Prognosis

Giampaolo Niccoli,* Rocco A. Montone,* Borja Ibanez, Holger Thiele, Filippo Crea, Gerd Heusch, Heerajnarain Bulluck, Derek J. Hausenloy, Colin Berry, Thomas Stiermaier, Paolo G. Camici, Ingo Eitel
Subjects with MVO Who Underwent Postconditioning Had less MVO as Percentage of LV mass and Infarct Size

via reduced MVO may be an important, yet underreported benefit of postconditioning and may have contributed to the favorable remodeling effects we observed in this cohort. In a recent cell therapy study of similar STEMI patients, we reported that subjects with MVO experienced reduced recovery.

Table 7. Long-Term MRI Follow-Up of Subjects Who Had Microvascular Obstruction on Baseline MRI Scan

<table>
<thead>
<tr>
<th></th>
<th>Postconditioning (n=29)</th>
<th>Control (n=22)</th>
</tr>
</thead>
</table>

Postconditioning Did Not Modify Infarct Size or Myocardial Salvage 2-days Post-STEMI in Population Optimized to Show Benefit

![Graph showing AAR (g), Infarct Sz (g), MSI (%)]

Traverse, J. et al. Circ Res 2018
Ischemia-Reperfusion Injury

Clinical Track

NHLBI-Sponsored Randomized Trial of Postconditioning During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction