**MHIF FEATURED STUDY:**

**Exact Trial**

**DESCRIPTION:** an early phase, non-randomized study evaluating the safety of a single antegrade epicardial coronary artery infusion of NAN-101 in up to 12 subjects with non-ischemic cardiomyopathy and NYHA class III symptoms.

NAN-101 is a gene therapy product composed of a novel adeno-associated virus designed to target cardiomyocytes and deliver its payload of I-1c transgene. This genetic material provides code for an upstream inhibitor of the SERC2a pathway, which has been identified as a primary pathogenic mechanism in heart failure. The goal is to improve calcium cycling within the heart.

Preclinical studies have shown that constitutively activating I-1 within the failing rat heart improved not only contractility, but also reversed adverse remodeling by directly decreasing fibrosis and cardiac hypertrophy.

**CRITERIA LIST/QUALIFICATIONS:**

**Inclusion:**
- Chronic non-ischemic cardiomyopathy
- LVEF of 30% or less
- NYHA III

**Exclusion:**
- Ischemic cardiomyopathy
- Restrictive cardiomyopathy/infiltrative cardiomyopathy
- Renal failure

**CONDITION:** Non-Ischemic Cardiomyopathy

**PI:** Jay Traverse, MD

**RESEARCH CONTACTS:**
- Jake Jensen – jacob.jensen@allina.com | 612-863-3818
- Karl Thomas - karl.thomas@allina.com | 612-863-7493

**SPONSOR:** AskBio

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**DISCLOSURE INFORMATION**

- I have no financial relationships to disclose.
- I will discuss Investigative uses of Stem Cells
- I am NOT an cardiac MRI Expert !!
The Powerful Influence of Microvascular Obstruction (MVO) in Cardiovascular Clinical Trials

Jay H Traverse, MD
Minneapolis Heart Institute at Abbott Northwestern Hospital
University of Minnesota Medical School
Cardiovascular Cell Therapy Research Network (CCTRN)

Microvascular Obstruction (MVO)

- 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).
Persistent ST-Segment Elevation Following Successful PCI of LAD

MVO is represented by hypo-enhanced (orange) region inside the hyper-enhanced (yellow) infarct region
Early MVO – First Pass Perfusion MRI
Area of hypo-enhancement (2-min post contrast)

Late MVO –
hypo-enhanced region within Hyper-enhanced infarct zone
Secondary to accumulation of contrast 15-mins post-gadolinium.

89 y/o female with 20 hours of SOB and chest and shoulder tightness
Coronary Angiogram of Recent STEMI Patient

72 y/o Vietnamese Man with IDDM presents with several days of feeling ill with SOB and chest pressure
Coronary Angiogram Before and After PCI of LAD

Why does one patient develop significant MVO and the Other Doesn’t??

- Later presentation – < 1 day vs. 2-3 days
- pH = 7.31 with DKA
- Males vs. female
- High vs. low LVEDP
- Medications
- Endothelial Dysfunction
1025 STEMI Patients who received primary PCI.

Freedom from cardiac death CHF, recurrent MI.

MVO more powerful predictor than Infarct size

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>MO absent</th>
<th>MO present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Event (Days)</td>
<td>447</td>
<td>293</td>
</tr>
<tr>
<td>Time to Event (Days)</td>
<td>566</td>
<td>379</td>
</tr>
</tbody>
</table>


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

The Presence of MVO as Powerful as Infarct Size or LV function in Predicting Event-Free Survival

Multicenter Study from Germany Of 738 STEMI patients

Eitel, et al. JACC 2014

The Powerful Influence of MVO in CV Clinical Trial Results

- Ischemia / Reperfusion Injury - Postconditioning
- Stem Cell Therapy
- Circadian Basis of Ischemic Injury
Ischemia-Reperfusion Injury

Intraluminal and Extravascular Factors of Microvascular Injury Before, During and After Reperfusion

- Before occlusion
- During occlusion
- After reperfusion

- Diabetes Mellitus, Metabolic syndrome
- In-situ thrombosis
- Cellular plugging
- Embolization
- Vasospasm

- Hypercholesterolemia Inflammation
- Loss of vascular integrity
- Myocardial edema
- Hemorrhage

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


Postconditioning

“*The application of brief periods of ischemia during the initial phase of reperfusion.*”

- Resulted in 50% reduction in Infarct Size in the Dog. Must be administered within 1 minute of reperfusion. (Zhao ZQ, et al. AJP 2003).
- Initial early positive small clinical trials have been tempered by larger negative Trials.
How do brief periods of reperfusion and ischemia result in myocardial protection?

Hypothesis:

1.) Repeated occlusions maintain acidosis to keep MPTP from opening.

2.) Delivery of O2 during reperfusion promotes ROS formation which activates kinases through redox signaling.

Cohen MV, Basic Res Cardiol 2008

Mechanisms of Postconditioning

- Activation of sarcolemmal G-protein-coupled receptors.
- Activation of RISK Pathway
- Inhibition of GSK3β increases threshold for MPTP opening

Heusch Circ 2008;118:1919
• 58 patients with STEMI and TIMI 0 Flow w/o collaterals

• Randomized to CSA (2.5 mg/kg) vs NS prior to Reperfusion by PCI

• Patients had similar ischemic times, LVEF prior to PCI

Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction

Christophe Piot, M.D., Ph.D., Pierre Croisille, M.D., Patrick Staart, M.D., Hélène Thibault, M.D., Gilles Roufot, M.D., Ph.D., Nathan Newton, M.D., Rachid Elbelhiti, M.D., Thien Tn Cung, M.D., Eric Bonnefoy, M.D., Ph.D., Denis Angoulvant, M.D., Christophe Macia, M.D., Franck Raczka, M.D., Catherine Sportouch, M.D., Gerald Gahide, M.D., Gérard Finet, M.D., Ph.D., Xavier André-Foult, M.D., Didier Revel, M.D., Ph.D., Gilbert Kirikian, M.D., Ph.D., Jean-Pierre Monassier, M.D., Geneviève Deremeaux, M.D., Ph.D., and Michel Ovize, M.D., Ph.D.

CSA reduces infarct size by CK AUC.

CSA = 138,000 AU

Control = 248,000 AU

Piot et al NEJM 2008
CSA Reduces Infarct Size by cMRI (delayed hyperenhancement)

**CIRCUS – In Phase 3 study of 970 STEMI patients, CSA did not improve clinical outcomes or LV remodeling at one year.**

Used different formulation of CSA in CIRCUS compared to Positive Pilot Trial

Piot C, et al. NEJM 2008

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### Interventional Cardiology

**Ischemic Postconditioning During Primary Percutaneous Coronary Intervention**

The Effects of Postconditioning on Myocardial Reperfusion in Patients With ST-Segment Elevation Myocardial Infarction (POST) Randomized Trial

Joo-Yong Hahn, MD*; Young Bin Song, MD*; Eun Kyoung Kim, MD; Cheol Weong Yu, MD; Jung-Whan Bae, MD; Woo-Young Chung, MD; Seung-Hyuk Choi, MD; Jin-Ho Choi, MD; Jang-Ho Bae, MD; Kyung Joo An, MD; Jong-Seon Park, MD; Ju Hyeon Oh, MD; Sang-Wook Kim, MD; Jin-Yong Hwang, MD; Jae Kean Ryu, MD; Hun Sik Park, MD; Do-Sun Lim, MD; Hyeon-Cheol Gwon, MD

- 700 Korean patients with STEMI randomized to PostC +PCI vs. routine PCI.
- PC protocol = 4, 1-min occlusion / reperfusion
- 50% had thrombus aspiration prior to PostC protocol
- Primary endpoint = complete ST segment resolution by EKG.

**Results:** No difference in ST-seg resolution, blush grade or MACE between groups.

**Limitations:** Unlikely to have truly initiated “PC” protocol within 1 min of reperfusion given that 50% of patients had aspiration thrombectomy.
Ischemia-Reperfusion Injury

Clinical Track

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


HYPOTHESIS

The inconsistent finding of benefit in previous trials arises from issues of patient selection that may render Postconditioning ineffective.

These include:

- Prolonged ischemic times (> 6 hrs.)
- Collateral blood flow
- Occurrence of limited reperfusion (TIMI flow > 0)
- Failure to exclude patients with pre-infarction angina.
- Failure to perform postconditioning immediately upon reperfusion with PTCA balloon.
**Trial Design**

We designed a single-center trial funded by the NHLBI to definitively answer if postconditioning reduces infarct size and increases myocardial salvage by using an optimized patient population of STEMI patients presenting for primary PCI.

- Ischemic times between 1 and 6 hours
- 100% occlusion of major epicardial artery
- Exclusion of patients with PIA and collaterals
- cMRI measurements of infarct size and salvage
- Immediate initiation of PC upon reperfusion

**Trial Design (Cont)**

- STEMI patients admitted directly to cardiac catheterization laboratory as part of *LEVEL 1 Program*.
- First STEMI with 100% occlusion of major artery.

Consent obtained following initial angiography.

- Verbal consent followed by full informed consent within 24 hrs. (n=90).
- Emergency Waiver of Consent for remaining patients (BRANY IRB).

**Trial Design (Cont)**

**Postconditioning Protocol:**
- Four, 30-sec inflation / deflations upon immediate restoration of flow by guidewire.
- Thrombectomy mandated after PC protocol.
- Cardiac MRI performed 1 – 3 days post PCI and again at 3 and 12-months.

**Primary Endpoints:**
- Infarct size and Myocardial Salvage (AAR-IS)/AAR and MVO between PostC and Control group.

---

**Postconditioning Trial – Baseline Data**

<table>
<thead>
<tr>
<th></th>
<th>1298±1307</th>
<th>986±1263</th>
<th>810±1313</th>
<th>680±1124</th>
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<tbody>
<tr>
<td>coronary</td>
<td>65.5</td>
<td>32.1</td>
<td>20.1</td>
<td>19.5</td>
</tr>
<tr>
<td>intervention</td>
<td>21.3</td>
<td>29</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>1238±935</td>
<td>943±699</td>
<td>667±457</td>
<td>527±400</td>
</tr>
<tr>
<td></td>
<td>77.5</td>
<td>40.2</td>
<td>19.5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>21.5</td>
<td>29.9</td>
<td>40</td>
<td>45.8</td>
</tr>
</tbody>
</table>

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

Traverse, J. et al. Circ Res 2018

Long-Term Cardiac MRI Follow-up

The benefits of postconditioning may have been the protocol that permitted TIMI 1 flow and issues up to 12 hours. After initial reperfusion to TIMI 2 or 3 flow, aspiration thrombectomy was n over half the subjects and a new balloon, sized to was then procured to perform the postconditioning. This did not occur in our trial as the postconditioning was used to obtain initial reperfusion such that delay in starting the postconditioning algorithm.

Postconditioning in 249 patients when measured at 4 of follow-up. However, the postconditioning protocol was initiated until at least 1 minute after reperfusion could have rendered the postconditioning less effective. No measurements of LV volumes were reported. Addi all subjects received epifibatide and the influence of protein IIB IIIA receptor blockade in postconditioning unknown. Freixa et al observed no benefit of postcc on LVEF and change in LV volumes by cMRI in tients between 7 days and 6 months. However, the mean ischemic times of nearly 6 hours may have al any benefit of postconditioning.

Only one other previous postconditioning study formed MRI analysis at baseline and 12 months and f significant benefit of postconditioning on infarct size in 76 patients measured 6 to 9 days post-STEMI. E. Traverse J., et al. Circ Res 2018
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>
<tbody>
<tr>
<td>% of VAT</td>
<td>11.5±7.2</td>
<td>18.4±11.4</td>
</tr>
<tr>
<td>% of inferent mass</td>
<td>3.7±1.7</td>
<td>26.7±19.5</td>
</tr>
<tr>
<td>MVO</td>
<td>1.5±1.0</td>
<td>0.6±1.0</td>
</tr>
</tbody>
</table>

Subjects with MVO Who Underwent Postconditioning Had Improved LV Remodeling at One-Year

Table 6. Measurements of MVO on Baseline MRI Scan

March 1, 2019

Conclusions – Postconditioning and MVO

- Postconditioning did not reduce infarct size or myocardial salvage following STEMI despite the enrollment of a population optimized to show benefit.
- Postconditioning was associated with improved LV remodeling at 1-year.
- Subjects with MVO randomized to Postconditioning had smaller infarcts at baseline and less adverse LV remodeling at 1-year.
- Although Postconditioning did not reduce the number of patients with MVO, it reduced the amount of MVO mass and its percentage of infarct size.

The Role of MVO in Cell Therapy Trials

- The NHLBI and CCTRN-sponsored TIME Trial
  - 6 – month Data
  - 2 - Year Data
- Is the presence of MVO as a target for Cell Therapy?
120 Patients with Anterior STEMIs were Randomized to intracoronary cell therapy (150 million BMCs) vs. Placebo on Day 3 vs. Day 7 following Primary PCI.

Preliminary Communication

Effect of the Use and Timing of Bone Marrow Mononuclear Cell Delivery on Left Ventricular Function After Acute Myocardial Infarction

The TIME Randomized Trial

Context: While the delivery of cell therapy after ST-segment elevation myocardial infarction (STEMI) has been evaluated in previous clinical trials, the influence of the timing of cell delivery on the effect on left ventricular function has not been analyzed.

Objectives: To determine the effect of intracoronary administration of bone marrow mononuclear cell (BMC) delivery after STEMI on recovery of global and regional left ventricular function and whether timing of BMC delivery (3 days vs. 7 days after intervention) impacts LVEF.

Methods: A randomized, double-blind, placebo-controlled trial. Patients (n=156) had an ST-segment elevation myocardial infarction (STEMI) and were randomized to intracoronary administration of 150 million BMCs on day 3 vs. 7 following primary PCI.

Results: Primary Endpoint: Global

No difference in the change in LVEF between BMC (n=75) and Placebo (n=37) groups from baseline to 6 months.

Global LV Function — LVEF

No difference in the change in LVEF between BMC (n=75) and Placebo (n=37) groups from baseline to 6 months.

Mean: 45.2 vs. 44.5

Time After MI

Baseline 6 Mo Baseline 6 Mo
Results for both infarct zone and border zone wall motion were also not significant by therapy group for 3 days, 7 days, or overall.

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

Jay H. Traverse, MD
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
Two-Year Results of TIME

- 85 patients (BMC=58; Placebo=27) completed stipulated 2-year clinical and MRI Follow-up.
  - ICD implants (n=10)
  - Death (n=3)
  - Lost to Follow-up (n=7)
  - MRI contraindications (n=15)

Change in LV Ejection Fraction (%) over 2 Years

Change in Infarct Size (g) over 2 Years

Change in LV End-Diastolic Volume Index (ml / m²)
### 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

Change in LV Ejection Fraction over 2-years stratified by presence or absence of MVO

<table>
<thead>
<tr>
<th>Time</th>
<th>MVO</th>
<th>No MVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
</tbody>
</table>


Change in Infarct Size (g) over 2 Years Stratified by Presence or Absence of MVO

<table>
<thead>
<tr>
<th>Time</th>
<th>MVO</th>
<th>No MVO</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
</tbody>
</table>
Conclusions

• Intracoronary delivery of autologous BMCs 3 or 7 days following STEMI did not improve LV function or attenuate LV remodeling at 6 months.

• LV function, volumes and infarct size remain stable between 6 months and 2-years.

• The presence of MVO is associated with significant reductions in the recovery of LV function, greater adverse LV remodeling and increased need for ICD implants (8 vs. 2).
A Circadian Basis for Onset of Myocardial Infarction, Tolerance to Ischemia and MVO

Light entrains the master pacemaker in the SCN which in turn synchronizes extra–SCN and peripheral clocks. The Core Clock consists of series of transcription / translation feedback loops that synchronize diverse metabolic processes.

Circadian Regulation of Vascular Tone

Paschos GK and FitzGerald GA. Circ Res 2010;106:833

STIMI

STEMI signs or symptoms (176), such as severe headache, sweating, or emesis at onset (P < 0.05).

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

The key pathophysiologic process underlying SCD, MI, and stroke due to thrombosis is rupture of vulnerable atherosclerotic plaques (9). Such disruptions expose the subendothelial collagen and tissue factor, which in turn serve as the stimulant 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 elastic fibers results in an increase in platelet aggregation.

Platelet Aggregation

ADP and Epinephrine at 3-Hour Intervals during a 24-Hour Period

ADP and epinephrine at 3-hour intervals during a 24-hour period showed the presence of a significant morning (6 to 9 a.m.) increase during the period from 6 to 9 a.m., the minimum concentration of platelet aggregation decreased (platelet aggregability increased) from 4.7±0.3 μmol/L of epinephrine required decreased from 3.2%. The increase in aggregability in response to ADP at the threshold concentration increased by 19%, from 22.4 to 48.7 percent (P<0.01), as did the rise in aggregability in response to ADP at the threshold concentration (P<0.02). The increase in aggregability in response to ADP at the threshold concentration increased by 19%.
WT = 3.5 x greater infarct size following 45-min LAD occlusion vs. Clock Mutant at the sleep to wake transition associated with nadir in phosphorylation of Akt and glycogen synthase kinase-3β (GSK-3β).

Lefer DJ Circ Res 2010;106:430

Circ Res 2012;110:105-110
Circadian Basis of Ischemic Tolerance in Humans

- 1031 patients presenting with ST elevation and ischemic time between 1 and 6 hrs
  - 568 = TIMI flow >0 or collateral filling of infarct vessel
  - 104 = preinfarction angina or postconditioning
  - 72 = CABG or prior MI
  - 70 = defibrillation or CPR
  - 44 = no documented peak CK
  - 6 = artery not opened
  - 2 = stent thrombosis within 72 hrs
- 165 patients included in analysis

Infarct Size by Cardiac Enzymes (CK) Peak at 1 AM onset of chest pain and 5 AM onset of Reperfusion with peak being 82% greater than trough

- LVEF measured 2-days post-STEMI correlated with time of onset of STEMI (Peak LVEF 7% > trough)
- Data supported by subgroup (n=45) of patients who underwent Cardiac MRI and measurement of AAR and IS.
- These results were subsequently confirmed in several later analyses from Europe.
1.) Could There be a Circadian Basis for the Development of MVO in Setting of STEMI?

2.) Role of Extravascular Compressive Forces
We performed a retrospective chart review of 3 MRI-based clinical trials recently performed at MHIF that had previously measured MVO and infarct size. These included the NHLBI and CCTRN TIME Trial (n= 115), The MHI Stem cell Trial (n=40) and the MHI Postconditioning Trial (n= 169). For the Circadian Analysis we assessed the time of onset of STEMI into eight, three-hour intervals to determine if there was a time-dependence for the occurrence of MVO.

**Circadian Dependence of MVO Development based on time of onset of STEMI**

![Graph showing number of patient cases over time](image)
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).

Measurement of zero-flow pressure (Pzf) in maximally-dilated dog heart (adenosine) under normal and elevated LVEDP (CHF) as surrogate for Extravascular Compressive Forces

**MVO mass Increases with Infarct Size**

Bonfig N, et al. AHA Scientific Sessions 2019

**MVO Increases with LV Mass (LVH)**

Bonfig et al., AHA 2019
LVEDP is significantly Higher in STEMI Patients with MVO

MVO Absent - n=144 - 23 ± 8 mmHg

MVO Present - n=184 - 26 ± 8 mmHg

p < .001

MVO Remains the most important Remaining Target 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
Thank You!

IV Microbubbles exposed To high mechanical index Impulses from a diagnostic Ultrasound transducer Abrogates MVO and improves Outcomes in STEMI patients.
CONCLUSIONS

- The causes of MVO are diverse as is its time course.
- Treatment Options

- Obvious factors influencing MVO include:
  - Infarct size, ischemic duration, LV mass, Circadian
  - Ischemia-Reperfusion Injury and endothelial dysfunction
  - Role of interventions to reduce I/R injury
  - Extravascular compression and myocardial edema.
  - Intramyocardial hemorrhage

Microvascular Obstruction (MVO) – A New Target for Cell Therapy

Brunskill SJ, Eur J Heart Failure 2009

Schachinger V, et al. NEJM 2006
Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial

Jérôme Roncalli1, Frédéric Mouquet2, Christophe Piot1, Jean-Noël Trochu1, Philippe Le Corvoisier1, Yannick Neuder3, Thierry Le Tourneau3, Denis Agostini1, Virginia Gazotte1, Catherine Sportouch1, Michel Galinié1, Dominique Crochet1, Emmanuel Teiger1, Marie-Jeanne Richard1, Anne-Sophie Poile21, Jean-Paul Bregie2, Alain Manqué2, Didier Corrie1, Sophie Sicier1, Bernard Klein1, Angelo Parini1, Guillaume Lamirot1, Pierre Croisille1, Hélène Rouard1, Philippe Bourin8, Jean-Michel Nguyen3, Béatrice Delasalle1, Gérard Vametto1, Eric Van Belle1, and Patricia Lomarchand9

8F-FDG Imaging (PET) of Stem Cell Retention in Human Heart Following STEMI

Activity of injected stem cells (%) (10-40 million Peripheral MNCs by IC Injection)

<table>
<thead>
<tr>
<th>Organ</th>
<th>2 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium</td>
<td>1.12</td>
<td>1.1</td>
</tr>
<tr>
<td>Liver</td>
<td>23.6</td>
<td>19.3</td>
</tr>
<tr>
<td>Spleen</td>
<td>12.3</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Change in Ejection Fraction (%)  
Stratified by Treatment and Presence of MVO

![Bar chart showing change in ejection fraction stratified by treatment and presence of MVO.](image)

Change in LV End-Diastolic Volume (ml)  
Stratified by Treatment and Presence of MVO

![Bar chart showing change in LV end-diastolic volume stratified by treatment and presence of MVO.](image)
Change in LV End-Systolic Volume (ml)
Stratified by Treatment and Presence of MVO

MVO
No MVO

Baseline 6 Months
Baseline 6 Months

MVO mass increases with LV mass

LV mass (g)
MVO mass (g)

Bonfig N, et al. AHA Scientific Sessions 2019

Davidson S, et al. AHA 2018 Scientific Sessions