MHIF FEATURED STUDY:

Exact Trial

Coming Soon!

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Non-Ischemic Cardiomyopathy	Jay Traverse, MD	Jake Jensen – Jacob.Jensen@allina.com | 612-863-3818 Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493	AskBio

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 it's 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

DISCLOSURE INFORMATION

- I have no financial relationships to disclose.
- I will discuss Investigative uses of Stem Cells
- I am NOT an cardiac MRI Expert !!

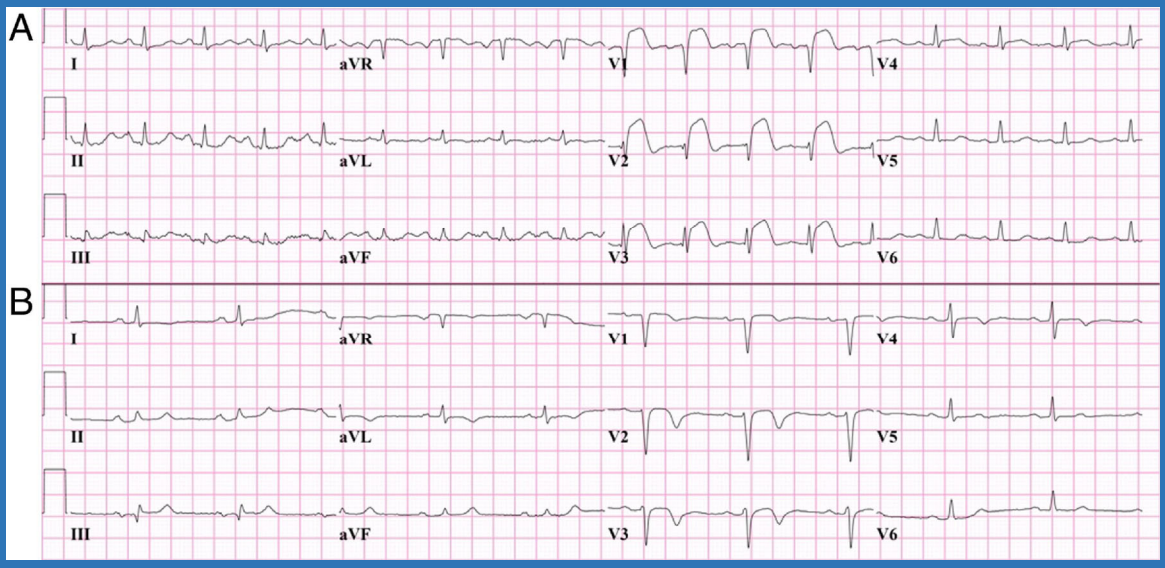
The Powerful Influence of Microvascular Obstruction (MVO) in Cardiovascular Clinical Trials

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)

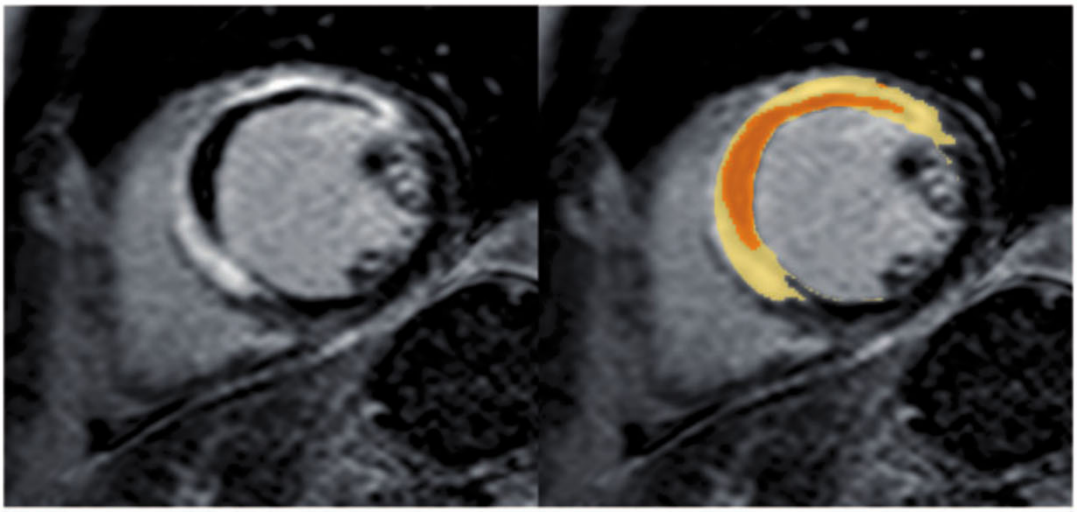
- Observed on cMRI in 40 -70% of STEMI patients.
- Manifested as persistent ST-elevation on EKG or as No-Reflow following PCI.
- Likely diverse etiologies including:
  - Distal athero-embolic debris and platelet and WBC clumping
  - Microvascular dysfunction secondary to I / R injury.
  - Extrinsic compression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

Persistent ST-Segment Elevation Following Successful PCI of LAD



Bekkers s, et al. JACC 2010

MVO is represented by hypo-enhanced (orange) region inside the hyper-enhanced (yellow) infarct region



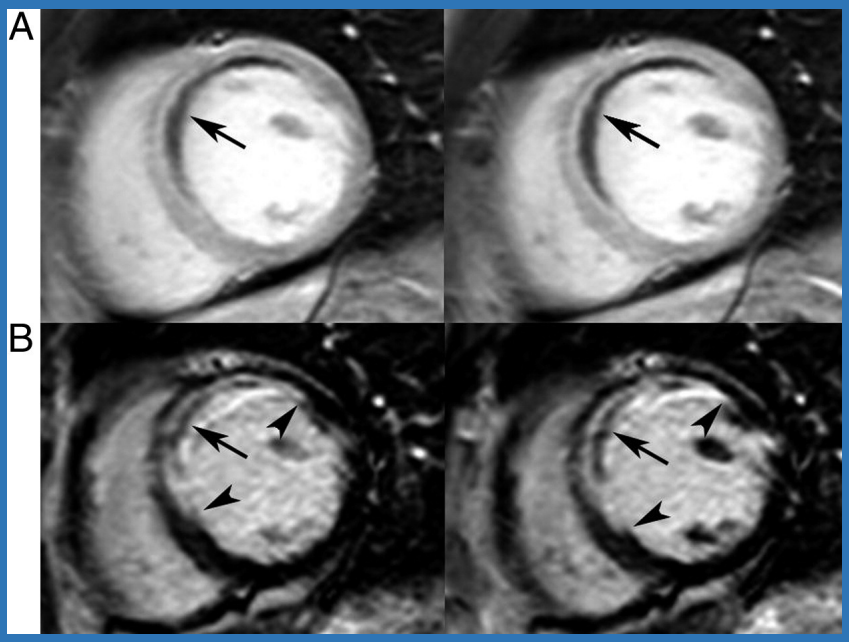
De Waha S., et al. Eur Heart J 2017

Early MVO – First Pass Perfusion MRI

Area of hypo-enhancement (2-min post contrast)

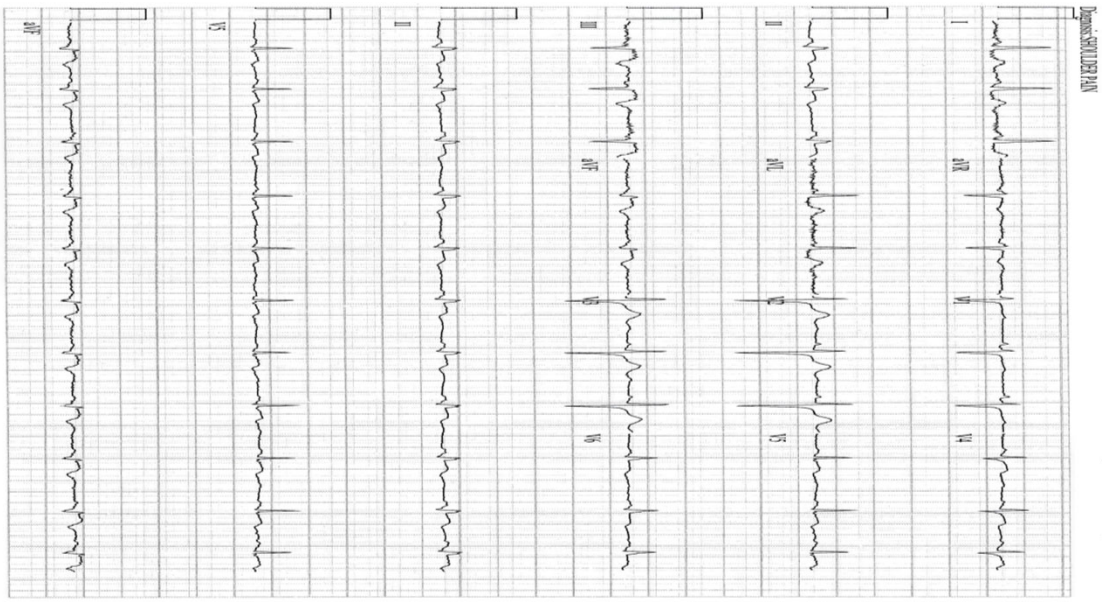
Late MVO –

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

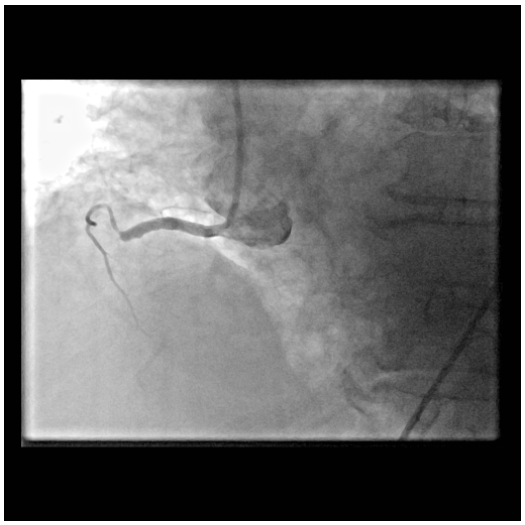


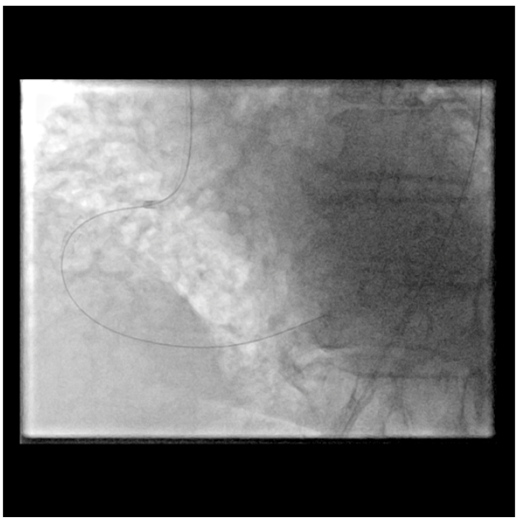
Bekkers s, et al. JACC 2010

89 y/o female with 20 hours of SOB and chest and shoulder tightness

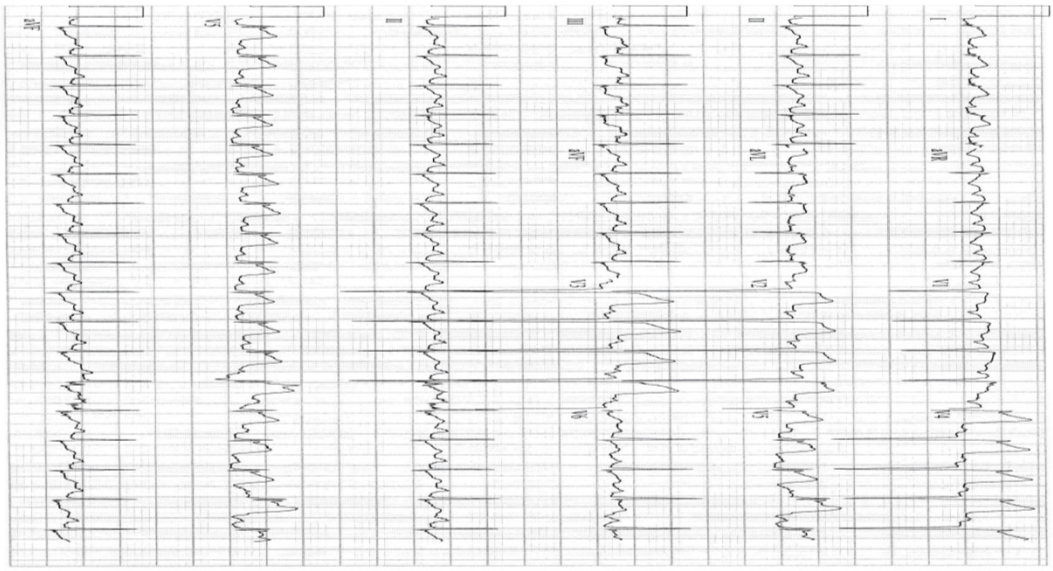


Coronary Angiogram of Recent STEMI Patient

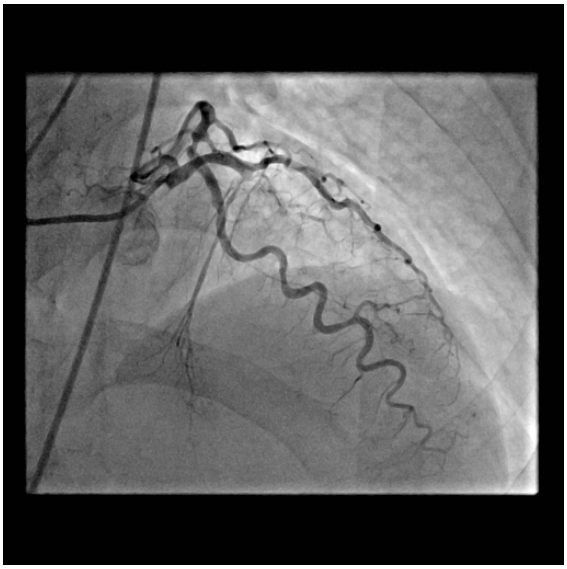


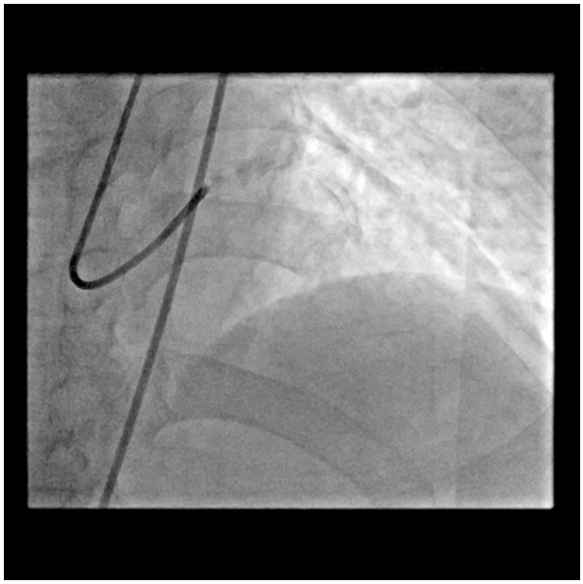


72 y/o Vietnamese Man with IDDM presents with several days of feeling ill with SOB and chest pressure



Coronary Angiogram Before and After PCI of LAD





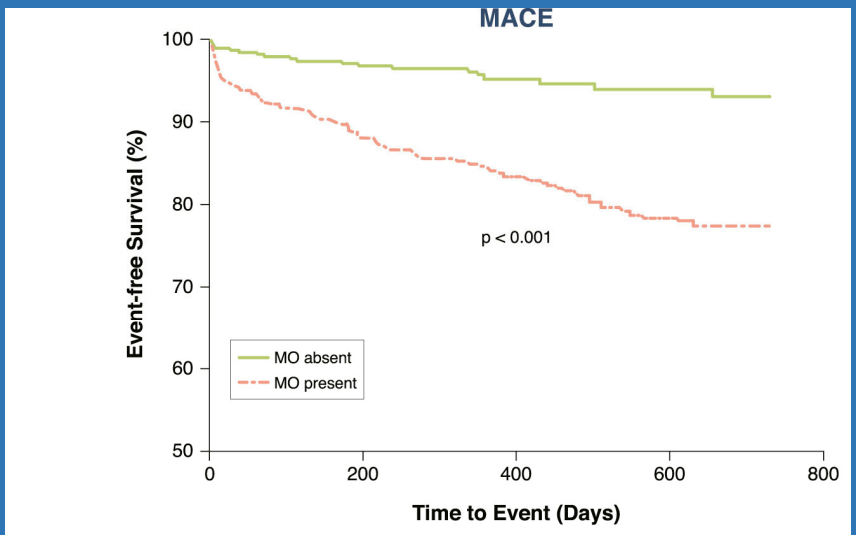
Why does one patient develop significant MVO and the Other Doesn't ??

- 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.

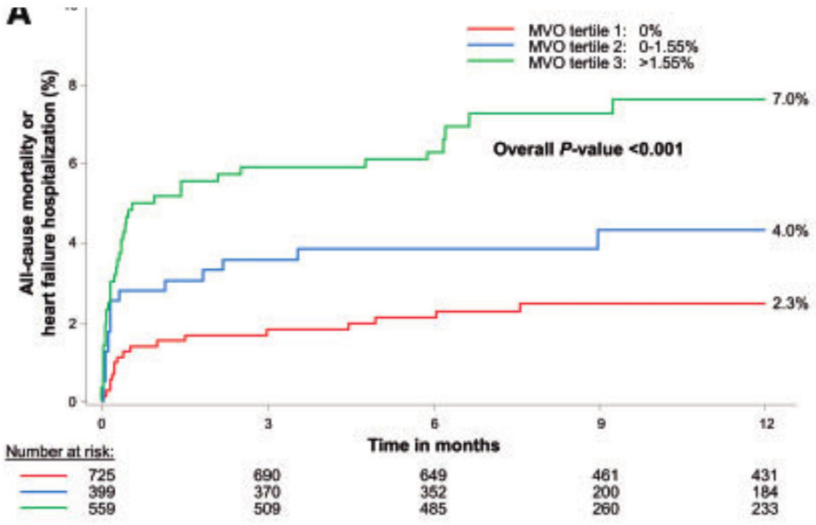
MVO more powerful predictor than Infarct size



Number at Risk					
MO absent	447	293	161	119	93
MO present	566	379	256	168	114

Van Kranenburg M, et al. JACC Imag. 2014

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

De Waha S., et al. Eur Heart J 2017

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

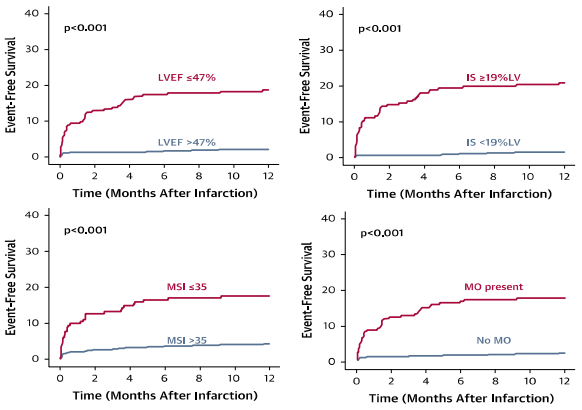


FIGURE 4 Event-Free Survival According to IS, Myocardial Salvage Index, LVEF, and MO

Kaplan-Meier curves showing the risk of cardiac events, stratified by the size of the infarct (IS), the myocardial salvage index (MSI), left ventricular ejection fraction (LVEF), and the presence of microvascular obstruction (MO). LV = left ventricle.

Multicenter Study from Germany Of 738 STEMI patients

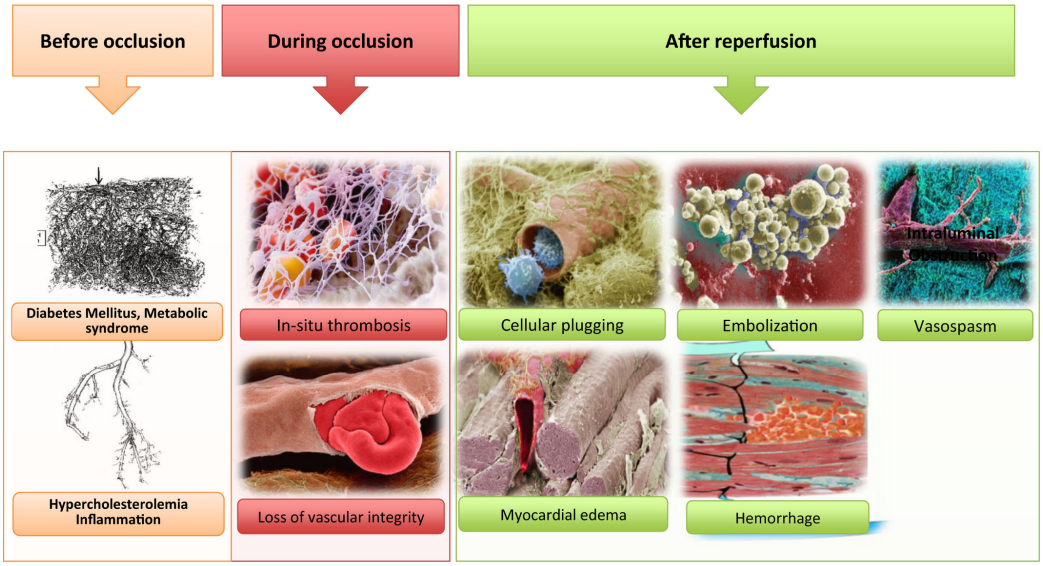
Eitel, et al. JACC 2014

The Powerful Influence of MVO in CV Clinical Trial Results

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

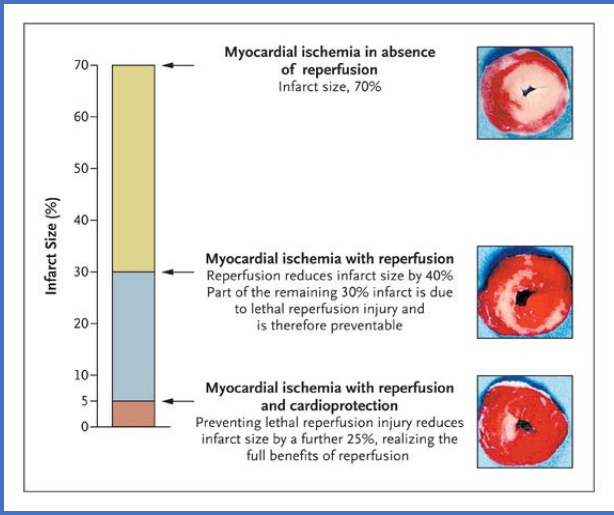
Ischemia-Reperfusion Injury

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



Sezar et al. JAHA 2018

Contribution of Lethal Reperfusion Injury Contributes up to 40% of Final Infarct Size



Yellon DM, Hausenloy DJ. N Engl J Med 2007;357:1121-1135.

The NEW ENGLAND JOURNAL of MEDICINE

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?

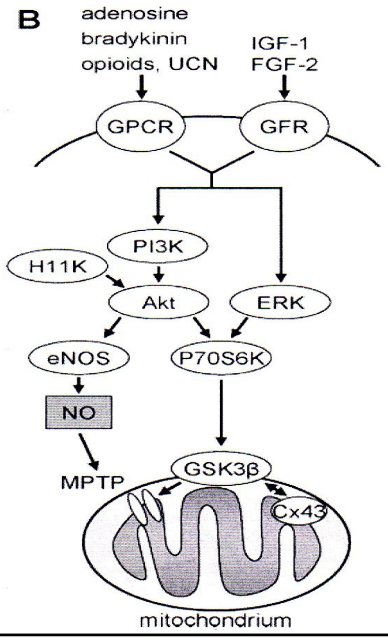
Hypothesis:

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

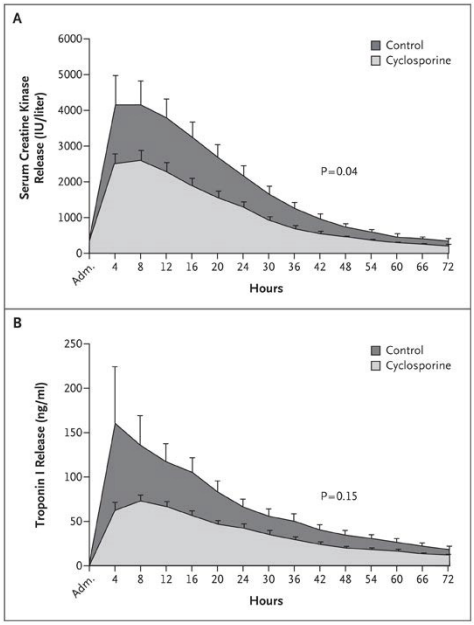
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction

Christophe Piot, M.D., Ph.D., Pierre Croisille, M.D., Patrick Staat, M.D., Hélène Thibault, M.D., Gilles Rioufol, M.D., Ph.D., Nathan Mewton, M.D., Rachid Elbelghiti, M.D., Thien Tri 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-Fouët, M.D., Didier Revel, M.D., Ph.D., Gilbert Kirkorian, M.D., Ph.D., Jean-Pierre Monassier, M.D., Geneviève Derumeaux, M.D., Ph.D., and Michel Ovize, M.D., Ph.D.

- 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



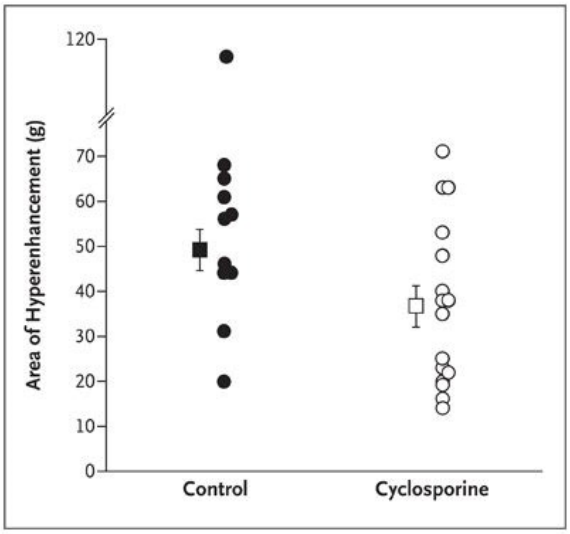
CSA reduces infarct Size by CK AUC.

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.
- Cung TT, et al. NEJM 2015.

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

Piot C, et al. NEJM 2008

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 Woong Yu, MD; Jang-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

Jay H. Traverse, Cory M. Swingen, Timothy D. Henry, Jane Fox, Yale L. Wang, Ivan J. Chavez, Daniel L. Lips, John R. Lesser, Wesley R. Pedersen, Nicholas M. Burke, Akila Pai, Jana L. Lindberg, Ross F. Garberich

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 repefusion 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

Allina Health ABBOTT NORTHWESTERN HOSPITAL | MINNEAPOLIS HEART INSTITUTE | Minneapolis Heart Institute Foundation Creating a world without heart disease

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).

Traverse JH. Circ Res 2016;119:1063-66.

Allina Health ABBOTT NORTHWESTERN HOSPITAL | MINNEAPOLIS HEART INSTITUTE | Minneapolis Heart Institute Foundation Creating a world without heart disease

Trial Design (Cont)

Postconditiong 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.

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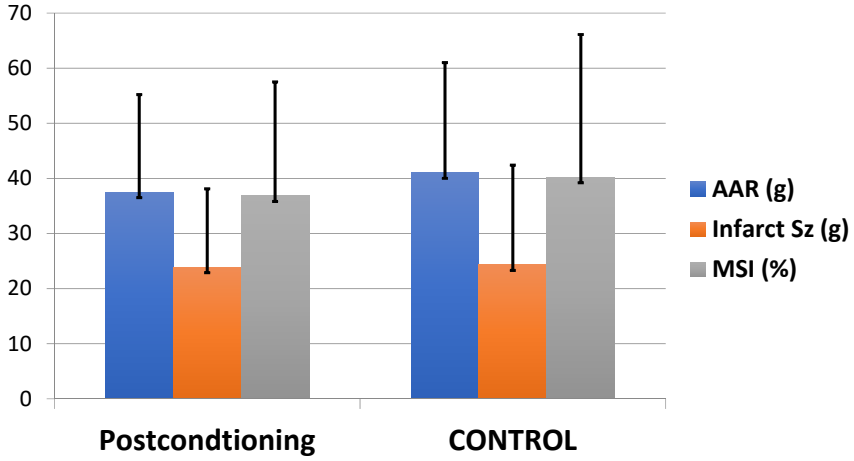
Postconditioning Trial – Baseline Data

	1298±1307	986±1263	810±1313	680±1124
	65.5	32.1	20.1	19.5
	21.3	29	40	45
)	1238±935	943±699	667±457	527±400
	77.5	40.2	19.5	17
	21.5	29.9	40	45.8

oronary intervention.

Traverse J., et al. Circ Res 2018

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

ıerence between the 2 groups at a mean follow-up
hs. In a subgroup of patients that underwent cMRI
=358) at day 1 and at 3 months, there was no dif-
infarct size, myocardial salvage, MVO, or LVEF.
ths, LVEF by echocardiography was higher in the
oning group versus control (52.7% versus 50.8%).
he benefits of postconditioning may have been
the protocol that permitted TIMI 1 flow and is-
ıes up to 12 hours. After initial reperfusion to
e TIMI 2 or 3 flow, aspiration thrombectomy was
ın 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 postcondition-
ı was used to obtain initial reperfusion such that
o delay in starting the postconditioning algorithm.

postconditioning in 249 patients when measured at 4
of follow-up.[27] However, the postconditioning protc
not initiated until at least 1 minute after reperfusio
could have rendered the postconditioning less effecti
no measurements of LV volumes were reported. Addi
all subjects received eptifibatide and the influence o
protein IIB IIIA receptor blockade in postconditioning
unknown. Freixa et al[29] observed no benefit of postcc
ing on LVEF and change in LV volumes by cMRI i
tients between 7 days and 6 months. However, the pr
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[30] and f
significant benefit of postconditioning on infarct size
in 76 patients measured 6 to 9 days post STEMI. F

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,[26] 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

	Postconditioning (n=29)		Control (n=22)	

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

AAR indicates area-at-risk; LV, left ventricular; and MVO, microvascular obstruction. *P=0.05.

	MVO			
	MVO mass, g	% of LV Mass	% of Infarct Size	% of AAR
Postconditioning	9.6±10.0	6.0±5.5	30.5±19.5	26.7±16.8
Control	11.5±7.2	8.4±4.1	37.1±17.0*	30.2±15.7

Table 6. Measurements of MVO on Baseline MRI Scan

776 Circulation Research March 1, 2019

Traverse J., et al. Circ Res 2018

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?

PRELIMINARY COMMUNICATION

ONLINE FIRST

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

The TIME Randomized Trial

Jay H. Traverse, MD; Timothy D. Henry, MD; Carl J. Pepine, MD; James T. Willerson, MD; David X. M. Zhao, MD; Stephen G. Ellis, MD; John R. Forder, PhD; R. David Anderson, MD, MS; Antonis K. Hatzopoulos, PhD; Marc S. Penn, MD, PhD; Emerson C. Perin, MD, PhD; Jeffrey Chambers, MD; Kenneth W. Baran, MD; Ganesh Raveendran, MD; Charles Lambert, MD, PhD; Amir Lerman, MD; Daniel L. Simon, MD; Douglas E. Vaughan, MD; Dejian Lai, PhD; Adrian P. Gee, PhD; Doris A. Taylor, PhD; Christopher R. Cogle, MD; James D. Thomas, MD; Rachel E. Olson, RN, MS; Sherry Bowman, RN; Judy Francescon, RN; Carrie Geither, RN; Eileen Handberg, PhD; Casey Kappenman; Lynette Westbrook, RN; Linda B. Piller, MD, MPH; Lara M. Simpson, PhD; Sarah Baraniuk, PhD; Catalin Loghin, MD; David Aguilar, MD; Sara Richman; Claudia Zierold, PhD; Daniel B. Spoon, MD; Judy Bettencourt, MPH; Shelly L. Sayre, MPH; Rachel W. Vojvodic, MPH; Sonia I. Skarlatos, PhD; David J. Gordon, MD, PhD; Ray F. Ebert, PhD; Minjung Kwak, PhD; Lemuel A. Moyé, MD, PhD; Robert D. Simari, MD; for the Cardiovascular Cell Therapy Research Network (CCTRN)

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 autologous 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 reperfusion) influences this effect.

Design, Setting, and Patients A randomized, 2 × 2 factorial, double-blind, placebo-controlled trial, Timing In Myocardial infarction Evaluation (TIME) enrolled 120 patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 45%) after successful primary percutaneous coronary intervention (PCI) of anterior STEMI between July 17, 2008, and November 15, 2011, as part of the Cardiovascular Cell Therapy Research Network sponsored by the National Heart, Lung, and Blood Institute.

Interventions Intracoronary infusion of 150 × 10^6 BMCs or placebo (randomized 2:1) within 12 hours of aspiration and cell processing administered at day 3 or day 7 (randomized 1:1) after treatment with PCI.

Main Outcome Measures The primary end points were change in global (LVEF) and regional (wall motion) left ventricular function in infarct and border zones at 6 months measured by cardiac magnetic resonance imaging and change in left ventricular function as affected by timing of treatment on day 3 vs day 7. The secondary end points included major adverse cardiovascular events as well as changes in left ventricular volumes and infarct size.

Results The mean (SD) patient age was 56.9 (10.9) years and 87.5% of participants were male. At 6 months, there was no significant increase in LVEF for the BMC group (45.2% [95% CI, 42.8% to 47.6%] to 48.3% [95% CI, 45.3% to 51.3%]) vs the placebo group (44.5% [95% CI, 41.0% to 48.0%] to 47.8% [95% CI, 43.4% to 52.2%]) ($P = .96$). There was no significant treatment effect on regional left ventricular function observed in either infarct or border zones. There were no significant differences in change in global left ventricular function for patients treated at day 3 (−0.9% [95% CI, −6.6% to 4.9%], $P = .76$) or day 7 (1.1% [95% CI, −4.7% to 6.9%], $P = .70$). The timing of treatment had no significant effect on regional left ventricular function recovery. Major adverse events were rare among all treatment groups.

Conclusion Among patients with STEMI treated with primary PCI, the administration of intracoronary BMCs at either 3 days or 7 days after the event had no significant effect on recovery of global or regional left ventricular function compared with placebo.

Trial Registration clinicaltrials.gov Identifier: NCT00684021

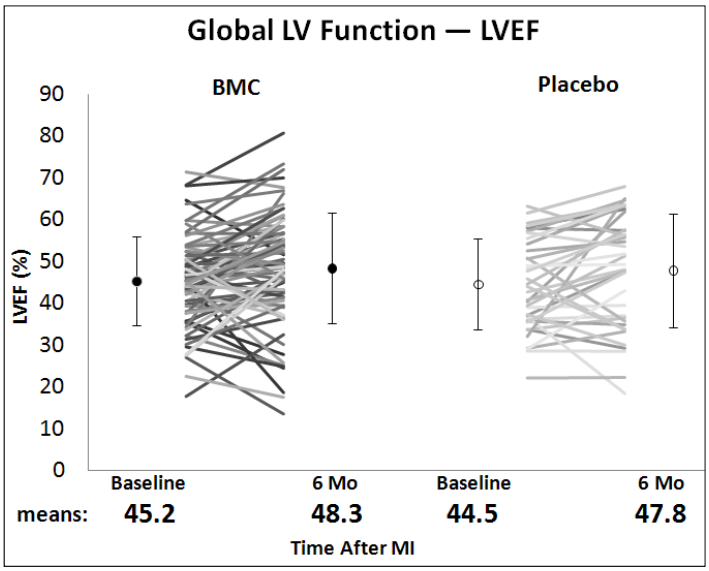
JAMA. 2012;308(22):2380-2389
Published online November 6, 2012. doi:10.1001/jama.2012.28726 www.jama.com

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.

Traverse, J., et al. JAMA 2012

Primary Endpoint: Global

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



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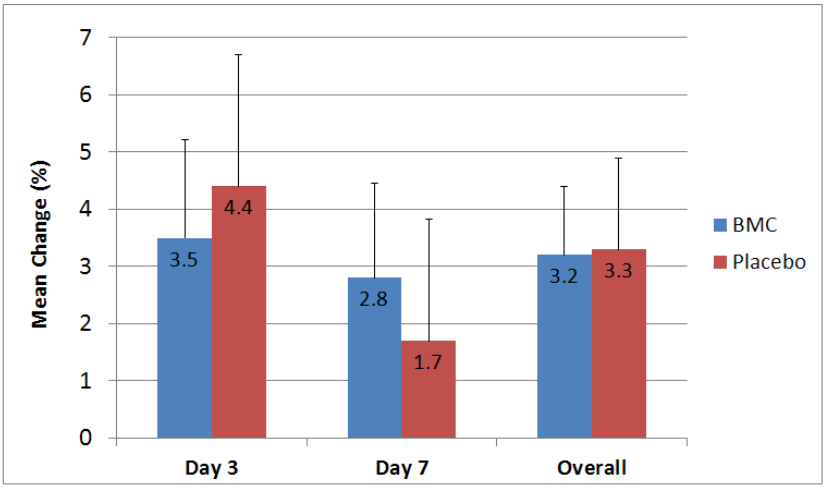
Effect of Delivery Timing on the Change from Baseline to Six Months for LVEF

LVEF (%)



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

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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

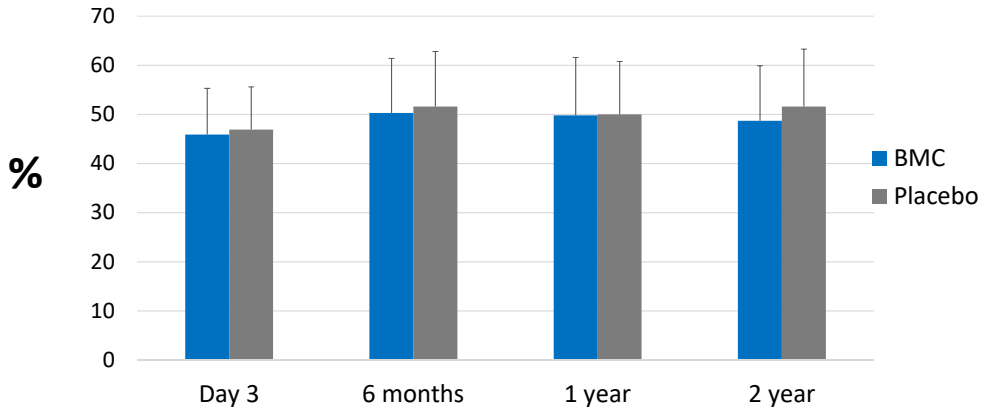
Two-Year Results of TIME

- 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)

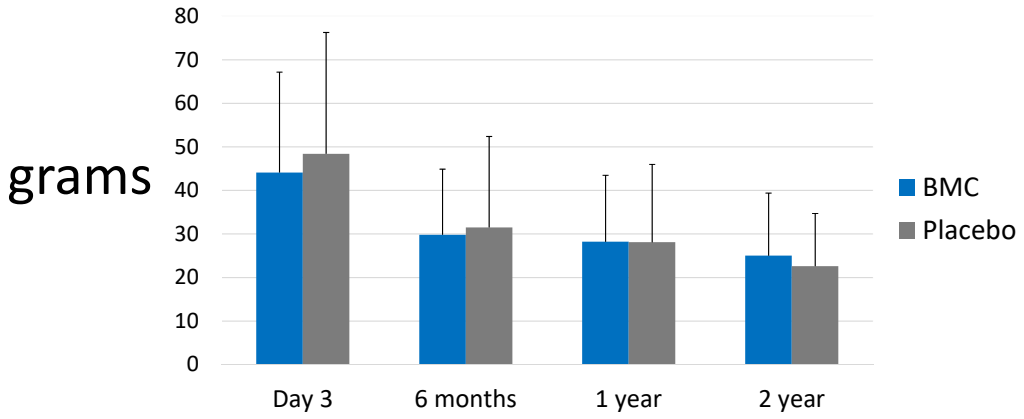
43

Change in LV Ejection Fraction (%) over 2 Years



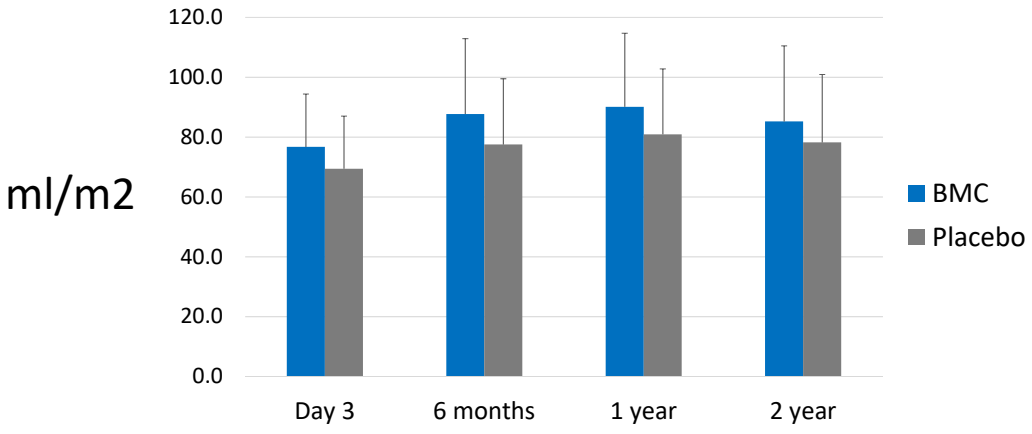
Traverse J, et al. Circ Res 2018

Change in Infarct Size (g) over 2 Years



Traverse J, et al. Circ Res 2018

Change in LV End-Diastolic Volume Index (ml / m^2)



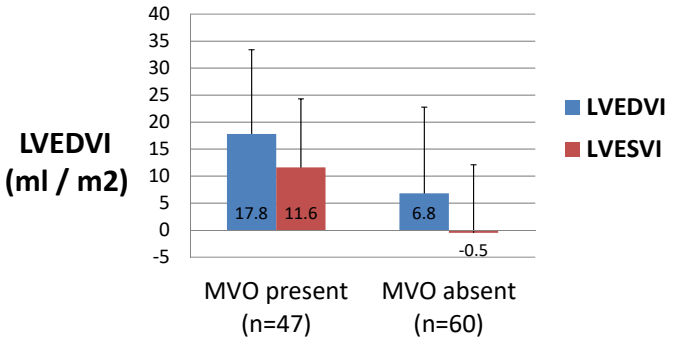
Traverse J, et al. Circ Res 2018

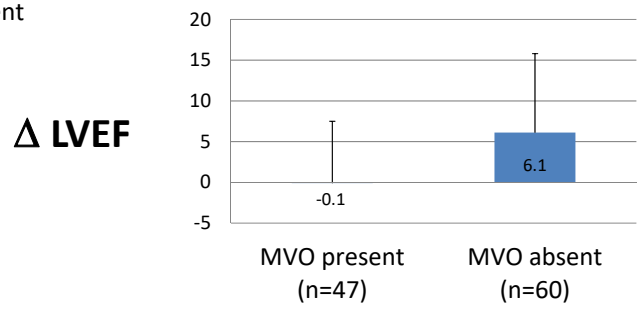
Baseline Data Stratified by MVO

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

47

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

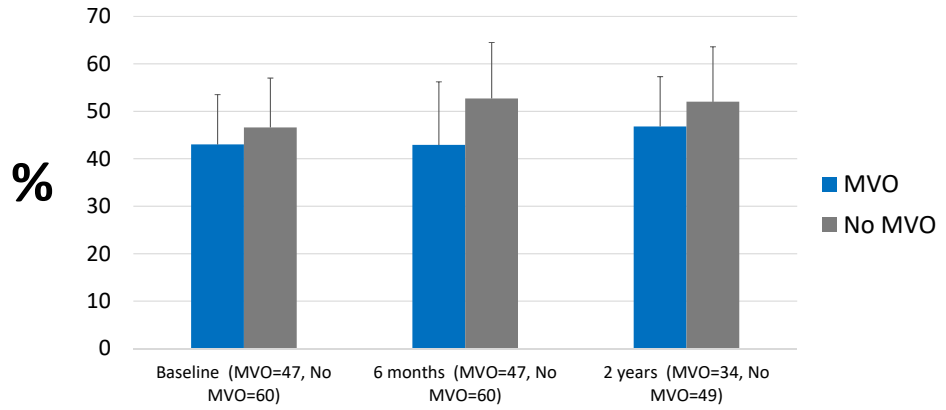




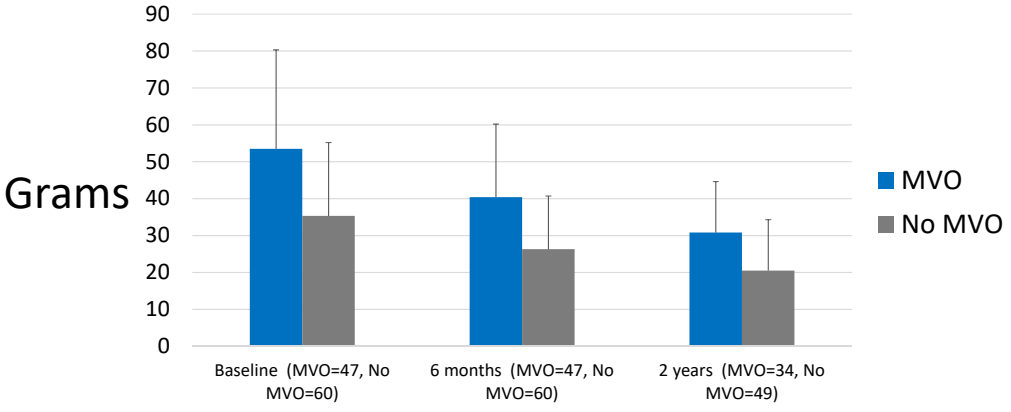
Traverse J, et al. Circ Res 2018

48

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

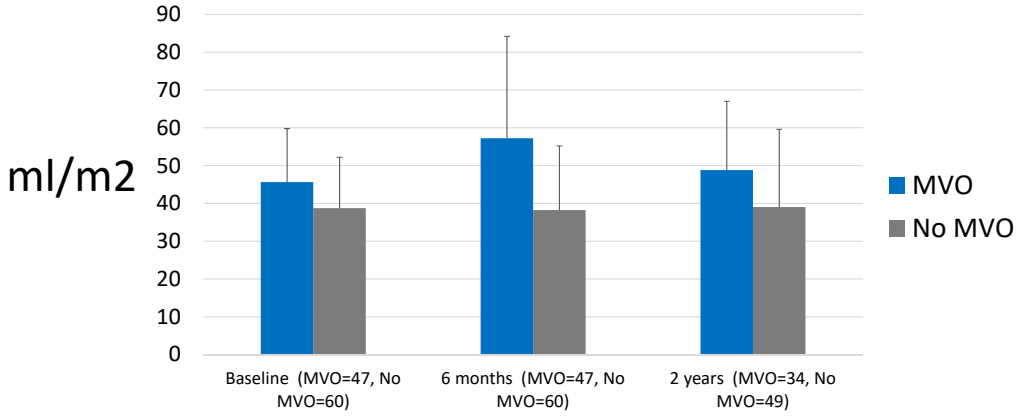


Change in Infarct Size (g) over 2 Years Stratified by Presence or Absence of MVO



Traverse J, et al. Circ Res 2018

Change in LVESVI over 2-Years Stratified by Presence or Absence of MVO



Traverse J, et al. Circ Res 2018

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).

52

A Circadian Basis for Onset of Myocardial Infarction, Tolerance to Ischemia and MVO

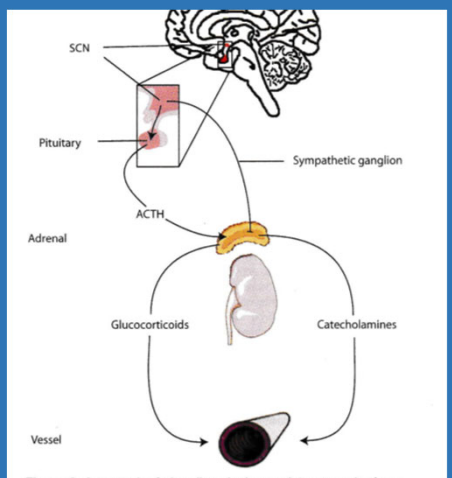
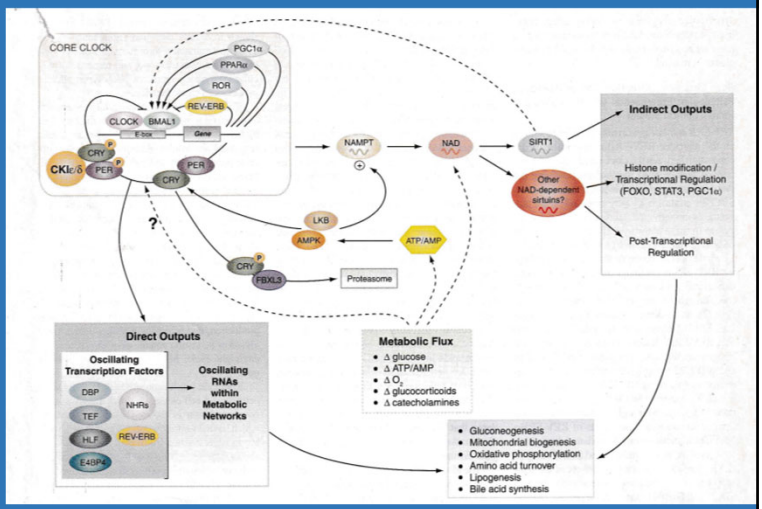


Figure 3. A network of circadian clocks regulates vascular function. The master oscillator in the SCN stimulates the release of glucocorticoids and catecholamines by the adrenal glands. Two

Circadian Regulation of Vascular Tone

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

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.



Bass J and Takahashi JS. Science 2010 330:1349

History of the triggering concept

In their original clinical description of acute myocardial infarction in 1910, Obraztsov and Strazhesko 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".[1] Their view, that infarction was triggered, was challenged in the 1930s as larger studies revealed that myocardial infarction often occurred without an obvious precipitating event. Authors argued for[2,3] and against[4,5] the belief that triggers were frequent. The controversy was eventually suspended for many years as Master's conclusion, based on retrospective questionnaires, that "coronary occlusion takes place irrespective of the physical activity being performed or the type of rest taken" gained widespread acceptance.[6] However, studies conducted with modern epidemiological methods and with new understanding of the pathogenesis of myocardial infarction indicate that the original concept of Obraztsov and

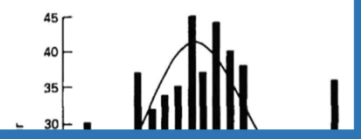
greatest obstacle to clarifying the role of potential trigger activities in the onset of infarction. To overcome the methodological problems involved in collection of such data, Maclure has developed a case crossover design; in this design, each patient serves as his or her own control for relatively recent activities.[10] A study funded by the National Heart, Lung and Blood Institute, currently uses this method. Over 2000 patients with infarction will be interviewed to determine their activities in the hours immediately before infarction onset and in a control period 24 hours earlier.

Epidemiological evidence that morning activities trigger onset

That myocardial infarction does not occur randomly throughout the day, but shows prominent circadian variation with increased morning frequency, supports the concept that daily activities are important triggers. Evidence obtained from the MILIS[7] (fig 1) and from the intravenous streptokinase in acute myocardial infarction (ISAM) study[11] (fig 2) clearly show that myocardial infarction is at least

STEMI

832 *Cohen, Muller*



Muller JE, et al. NEJM 1985:313

STROKE

signs or symptoms (171), such as severe headache, seizures, or emesis at onset ($P < .01$).

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.[7] Such disruption exposes intimal collagen and tissue factor, which in turn serve as foci 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 elas-

biphasic platelet agg
levels declined (ie, agg
9 AM. ADP concentrat
3.7 ± 0.6 μmol/L ($P <$
from 3.7 ± 0.8 to 1.8
This rise in platelet
nous, as it was due to
and participation in
among 10 subjects wh
no morning rise in
corded.
Another potential t
thrombosis is the mor
sure.[9] This increase is
echolamines upon assu
tend to increase corona
vasoconstriction could

Marler JR, et al. Stroke 1989:20

June 11, 1987
N Engl J Med 1987; 316:1514-1518
DOI: 10.1056/NEJM198706113162405

Article | Figures/Media

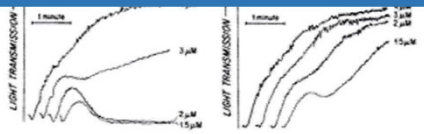
24 References
769 Citing Articles

Time

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

ed the presence of a significant morning (6 to 9 a.m.) incr
ng the period from 6 to 9 a.m., the minimum concentratio
ion decreased (platelet aggregability increased) from 4.7±0
n concentration of epinephrine required decreased from 3
f aggregation in response to ADP at the threshold concent
l 9 a.m., from 22±5 to 48±7 percent (P<0.01), as did the re
38±8 percent (P<0.02). The increase in aggregability betwe

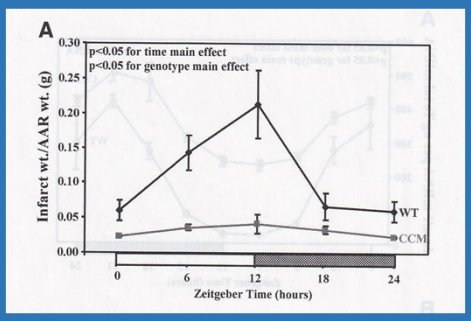
PLATELET AGGREGATION



ets in One Subject to Four Concentrations of ADP at 6 and

ng individual subjects was observed in the change in
ation tracings in a subject with an increase in respon

EPI- / NOREPINEPHRINE



WT = wild type
CCM – Genetically ablated clock genes

1.8-fold oscillation for phosphorylated [P]-GSK-3β, king at ZT0; $P<0.05$) and that phosphorylation is onically elevated in CCM hearts. In contrast, total Akt GSK-3β levels (as well as *gsk-3β* mRNA) are not erent between groups (Online Figures II and III). ortantly, negative correlations were observed for P-Akt P-GSK3β levels with infarct size (Figure 4C and 4D). contrast, phosphorylation of p70S6K (downstream of) did not correlate with infarct size (Online Figure IV).

Discussion

purpose of the present study was to determine whether tolerance varies over the course of the day and, if so, to

the day exhibit greatest infarct sizes at ZT14, similar to o observations in the mouse heart (greatest infarct size ZT12; Figure 2). ZT12 corresponds to the sleep-to-wa transition in the nocturnal rodent. As such, diurnal osci lations in the stimulus (ie, ischemia) and responsivene (ie, infarct development) are in phase.

Circadian dyssynchronization is classically associated wi cardiovascular morbidity and mortality. In humans, sh work significantly increases risk for cardiovascular disea development.[18] Similarly, subjecting cardiomyopathic ha sters to light/dark cycle manipulations augments early mo tality.[19] Genetic modulation of circadian clock timing, resu ing in subtle circadian dyssynchronization accelerates cardi

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).

Durgan et al. Circ Res 2010

ors or of the American Heart Association.
rom the Department of Surgery, Division of Cardiothoracic Surgery, ory University School of Medicine, Atlanta, Ga.

myocardial infarction at various times during the day. M surement of circulating biomarkers of myocardial injury left ventricular function would be necessary to assess

Lefer DJ Circ Res 2010;106:430

Evidence has recently emerged indicating that circadian clocks intrinsic to cardiac cells may contribute to time of day dependence of cardiovascular physiology. Multiple clock proteins appear to be regulated in a time-dependent manner in cardiomyocytes that may have profound effects on myocardial metabolism, function, and response to injury.[8] In animal models, the disruption of these circadian clocks has been implicated in the pathogenesis of various cardiovascular diseases.[9] Recently, Durgan et al[10] demonstrated that ischemia/reperfusion tolerance is dependent on the time of day of coronary occlusion. Using a

which the heart is subjected to ischemia influences subsequent infarct size and LV function in a cohort of patients with ST-segment elevation myocardial infarction (STEMI).

Methods

Study Design

A retrospective analysis was performed on all patients who were admitted to the Minneapolis Heart Institute at Abbott Northwestern Hospital from January 2006 through September 2010 as part of the level 1 acute myocardial infarction program. This is a regionalized transfer network for primary percutaneous coronary intervention (PCI) involving 31

Circ Res 2012;110:105-110

dently. Indeed, it is likely that it was these peripheral innate clocks that were responsible for the folding and unfolding of plant leaves described by d'Ortous. Most studies of these clocks have been carried out in the fungus *Neurospora*, in *Drosophila* and in a variety of rodents, but they have also been found in human cardiac tissue.[4] These peripheral circadian clocks are controlled by so-called "*CLOCK*" genes that have been found to control approximately 10% of all genes expressed in the mouse heart, which exhibit circadian rhythmicity.[5] This results in cyclic

such as a reduction of fibrinolytic activity. Indeed, in recent studies, Takeda et al[14] have shown that the thrombomodulin gene, a clock-controlled gene, is responsible for circadian oscillation of thrombomodulin mRNA and protein. Other studies have shown that the CLOCK genes regulate the expression of both plasminogen activator inhibitor-1 as well as the morning increase of platelet aggregability.[15] Thus, temporal changes in thrombogenicity can help to explain the circadian variation of the onset of cardiovascular events.

In this issue of *Circulation Research*, Reiter et al[16] describe

Circ Res 2012;110:6-7

Circadian Basis of Ischemic Tolerance in Humans

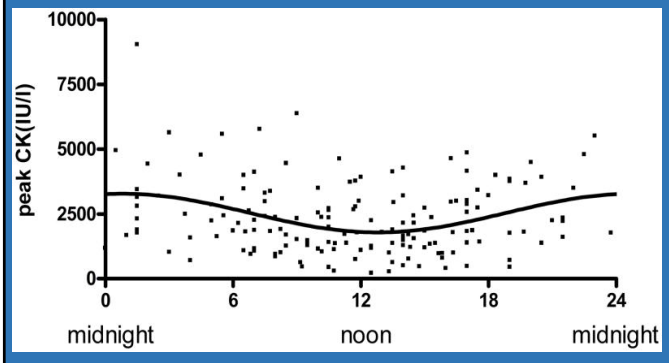
1031 patients presenting with ST elevation and ischemic time between 1 and 6 hrs

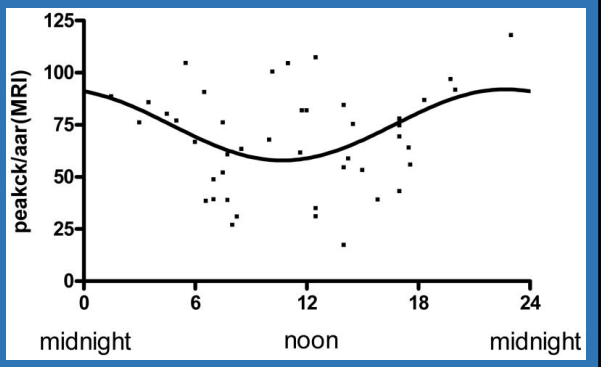
- → 568 = TIMI flow >0 or collateral filling of infarct vessel
- → 104 = preinfarction angina or postconditioning
- → 72 = CABG or prior MI
- → 70 = defibrillation or CPR
- → 44 = no documented peak CK
- → 6 = artery not opened
- → 2 = stent thrombosis within 72 hrs

165 patients included in analysis

Reiter R., et al. Circ Res 2015

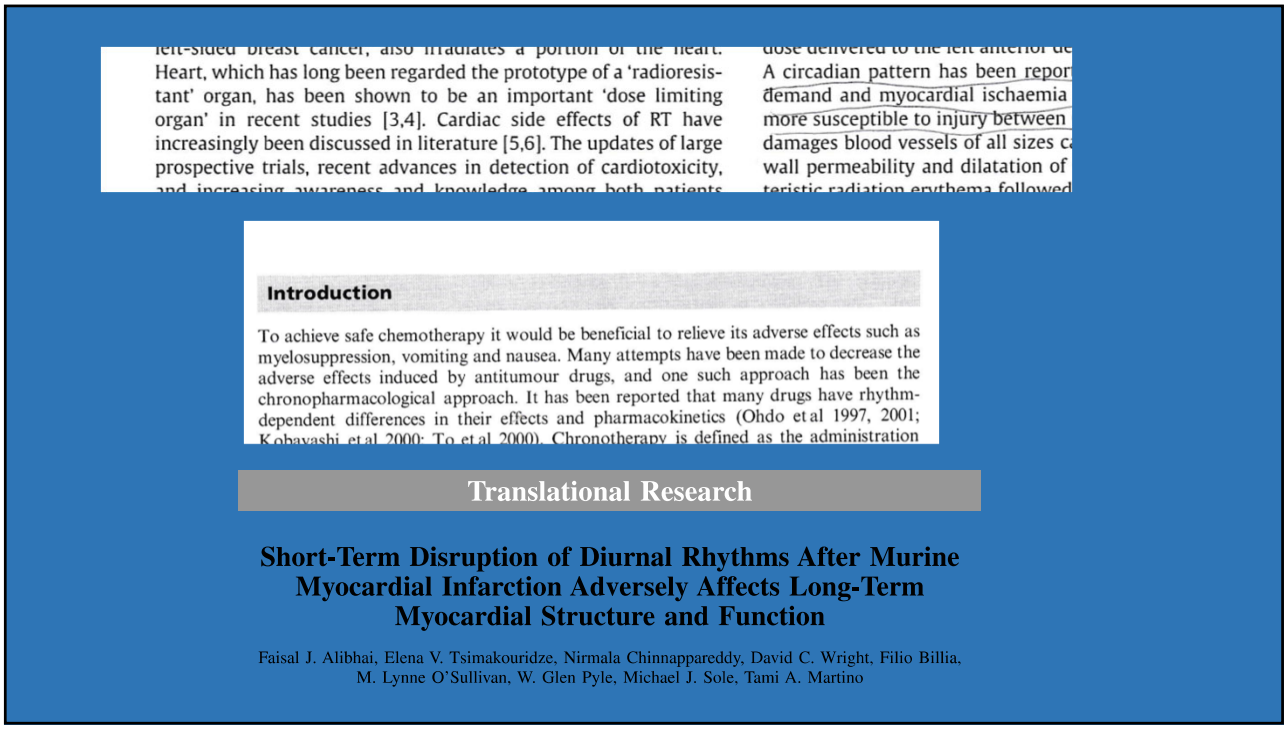
Infarct Size by Cardiac Enzymes (CK) Peak at 1 AM onset of chest pain and 5 AM onset of Reperfusion with peak being 82% greater than trough





- **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.**

Reiter R, et al. Circ Res 2012



left-sided breast cancer, also irradiates a portion of the heart. Heart, which has long been regarded the prototype of a 'radioresistant' organ, has been shown to be an important 'dose limiting organ' in recent studies [3,4]. Cardiac side effects of RT have increasingly been discussed in literature [5,6]. The updates of large prospective trials, recent advances in detection of cardiotoxicity, and increasing awareness and knowledge among both patients

dose delivered to the left anterior de
A circadian pattern has been repor
demand and myocardial ischaemia
more susceptible to injury between
damages blood vessels of all sizes c
wall permeability and dilatation of
teristic radiation erythema followed

Introduction

To achieve safe chemotherapy it would be beneficial to relieve its adverse effects such as myelosuppression, vomiting and nausea. Many attempts have been made to decrease the adverse effects induced by antitumour drugs, and one such approach has been the chronopharmacological approach. It has been reported that many drugs have rhythm-dependent differences in their effects and pharmacokinetics (Ohdo et al 1997, 2001; Kobayashi et al 2000; To et al 2000). Chronotherapy is defined as the administration

Translational Research

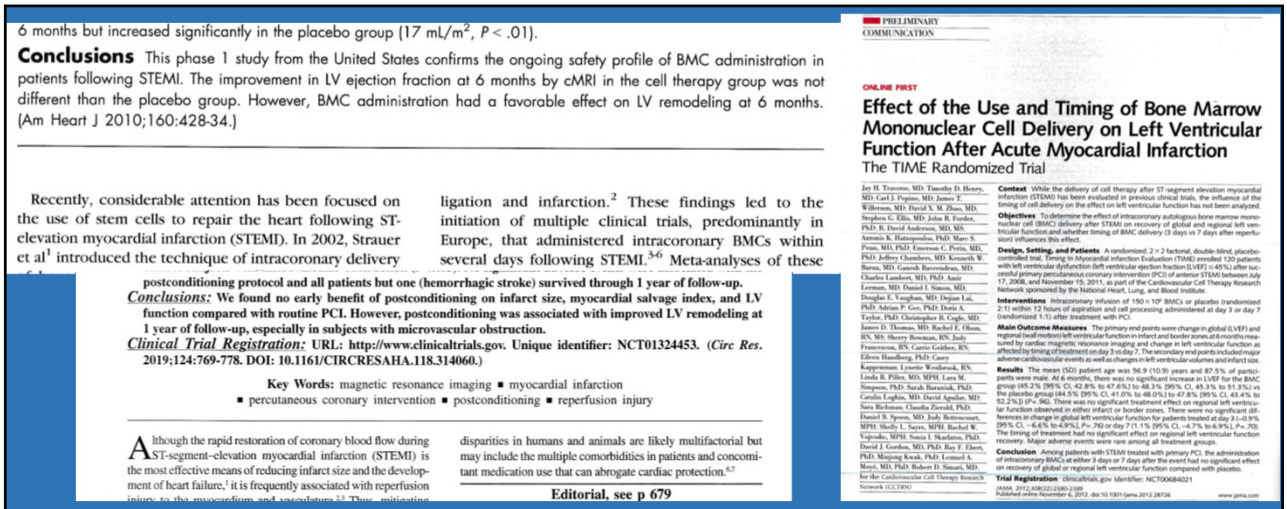
Short-Term Disruption of Diurnal Rhythms After Murine Myocardial Infarction Adversely Affects Long-Term Myocardial Structure and Function

Faisal J. Alibhai, Elena V. Tsimakouridze, Nirmala Chinnappareddy, David C. Wright, Filio Billia, M. Lynne O'Sullivan, W. Glen Pyle, Michael J. Sole, Tami A. Martino

Novel Mechanisms of MVO

1.) Could There be a Circadian Basis for the Development of MVO in Setting of STEMI?

2.) Role of Extravascular Compressive Forces



6 months but increased significantly in the placebo group (17 mL/m^2, $P < .01$).

Conclusions This phase 1 study from the United States confirms the ongoing safety profile of BMC administration in patients following STEMI. The improvement in LV ejection fraction at 6 months by cMRI in the cell therapy group was not different than the placebo group. However, BMC administration had a favorable effect on LV remodeling at 6 months. (Am Heart J 2010;160:428-34.)

Recently, considerable attention has been focused on the use of stem cells to repair the heart following ST-elevation myocardial infarction (STEMI). In 2002, Strauer et al[1] introduced the technique of intracoronary delivery

ligation and infarction.[2] These findings led to the initiation of multiple clinical trials, predominantly in Europe, that administered intracoronary BMCs within several days following STEMI.[3-6] Meta-analyses of these

postconditioning protocol and all patients but one (hemorrhagic stroke) survived through 1 year of follow-up.

Conclusions: **We found no early benefit of postconditioning on infarct size, myocardial salvage index, and LV function compared with routine PCI. However, postconditioning was associated with improved LV remodeling at 1 year of follow-up, especially in subjects with microvascular obstruction.**

Clinical Trial Registration: **URL: http://www.clinicaltrials.gov. Unique identifier: NCT01324453.** (*Circ Res.* 2019;124:769-778. DOI: 10.1161/CIRCRESAHA.118.314060.)

Key Words: magnetic resonance imaging ▪ myocardial infarction ▪ percutaneous coronary intervention ▪ postconditioning ▪ reperfusion injury

Although the rapid restoration of coronary blood flow during ST-segment–elevation myocardial infarction (STEMI) is the most effective means of reducing infarct size and the development of heart failure,[1] it is frequently associated with reperfusion

disparities in humans and animals are likely multifactorial but may include the multiple comorbidities in patients and concomitant medication use that can abrogate cardiac protection.[6,7]

Editorial, see p 679

PRELIMINARY COMMUNICATION

ONLINE FIRST

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 autologous 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 reperfusion) influences this effect.

Design, Setting, and Patients A randomized, 2 × 2 factorial, double-blind, placebo-controlled trial, Timing in Myocardial Infarction Evaluation (TIME) enrolled 120 patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 45%) after successful primary percutaneous coronary intervention (PCI) of anterior STEMI between July 17, 2008, and November 15, 2011, as part of the Cardiovascular Cell Therapy Research Network sponsored by the National Heart, Lung, and Blood Institute.

Interventions Intracoronary infusion of 150 × 10^6 BMCs or placebo (randomized 2:1) within 12 hours of aspiration and cell processing administered at day 3 or day 7 (randomized 1:1) after treatment with PCI.

Main Outcome Measures The primary end points were change in global (LVEF) and regional (wall motion) left ventricular function in infarct and border zones at 6 months measured by cardiac magnetic resonance imaging and change in left ventricular function as affected by timing of treatment on day 3 vs day 7. The secondary end points included major adverse cardiovascular events as well as changes in left ventricular volumes and infarct size.

Results The mean (SD) patient age was 56.9 (10.9) years and 87.5% of participants were male. At 6 months, there was no significant increase in LVEF for the BMC group (45.2% [95% CI, 42.8% to 47.6%] to 48.3% [95% CI, 45.3% to 51.3%] vs the placebo group (44.5% [95% CI, 41.0% to 48.0%] to 47.8% [95% CI, 43.4% to 52.2%]) ($P = .96$). There was no significant treatment effect on regional left ventricular function observed in either infarct or border zones. There were no significant differences in change in global left ventricular function for patients treated at day 3 (−0.9% [95% CI, −6.4% to 4.9%]; $P = .76$) or day 7 (1.1% [95% CI, −4.7% to 6.9%]; $P = .70$). The timing of treatment had no significant effect on regional left ventricular function recovery. Major adverse events were rare among all treatment groups.

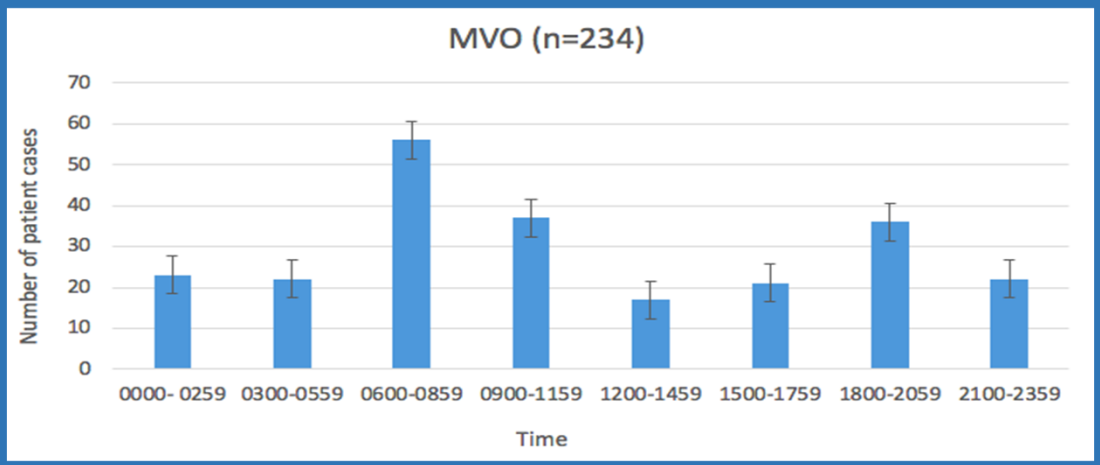
Conclusion Among patients with STEMI treated with primary PCI, the administration of intracoronary BMCs at either 3 days or 7 days after the event had no significant effect on recovery of global or regional left ventricular function compared with placebo.

Trial Registration clinicaltrials.gov Identifier: NCT00684021

JAMA. 2012;308(22):2380-2389. Published online November 6, 2012. doi:10.1001/jama.2012.28726

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



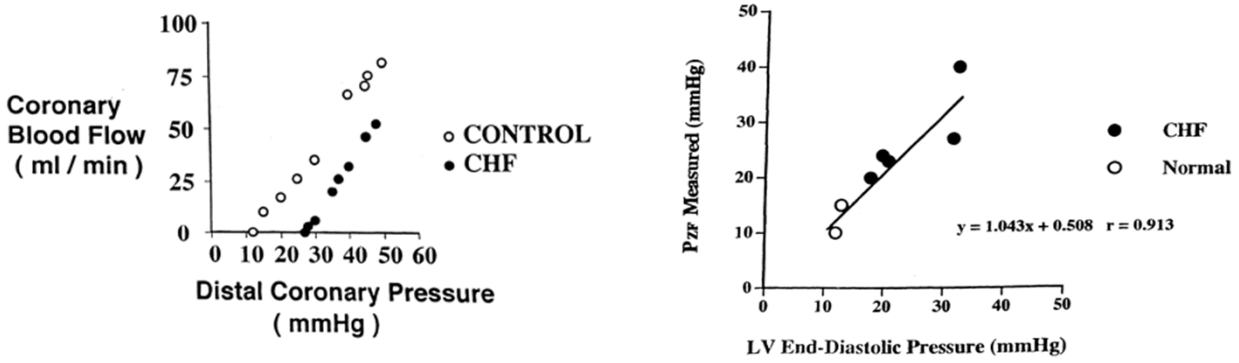
Bonfig N, et al AHA 2019

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).

Heinone I, et al. J Appl Physiol 2015.

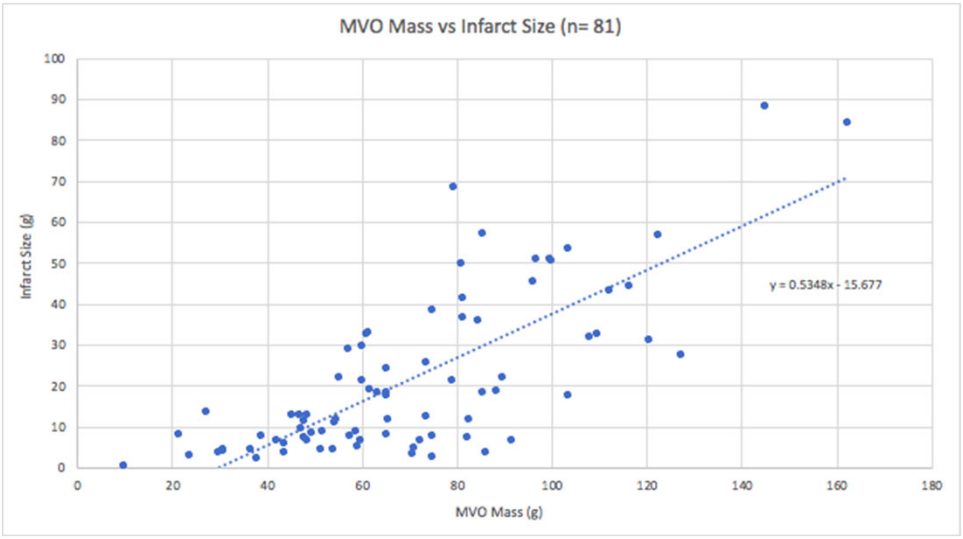
Measurement of zero-flow pressure (P_{zf}) in maximally-dilated dog heart (adenosine) under normal and elevated LVEDP (CHF) as surrogate for Extravascular Compressive Forces



Traverse JH, et al. Cardiovasc Res, Volume 52, Issue 3, December 2001, Pages 454–461, https://doi.org/10.1016/S0008-6363(01)00392-3.

OXFORD UNIVERSITY PRESS

MVO mass Increases with Infarct Size

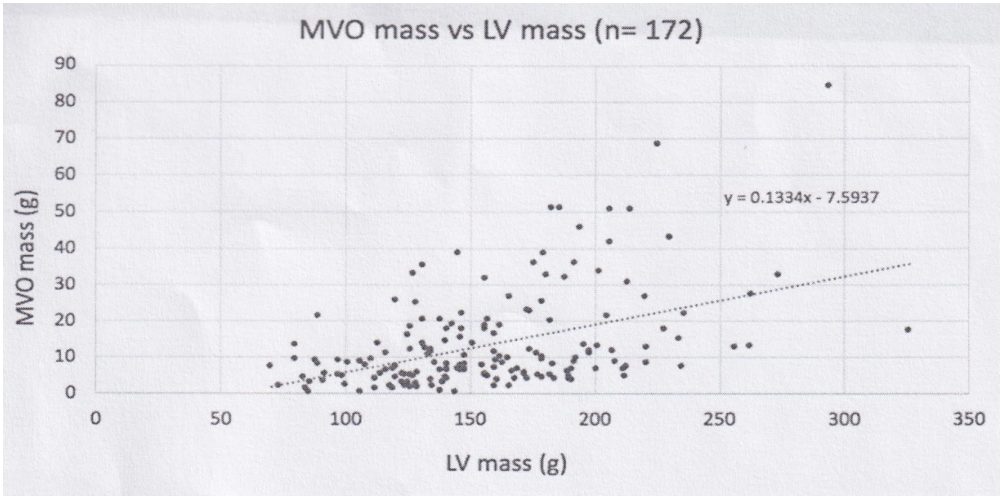


Infarct Size (g)

MVO Mass (g)

Bonfig N, et al. AHA Scientific Sessions 2019

MVO Increases with LV Mass (LVH)

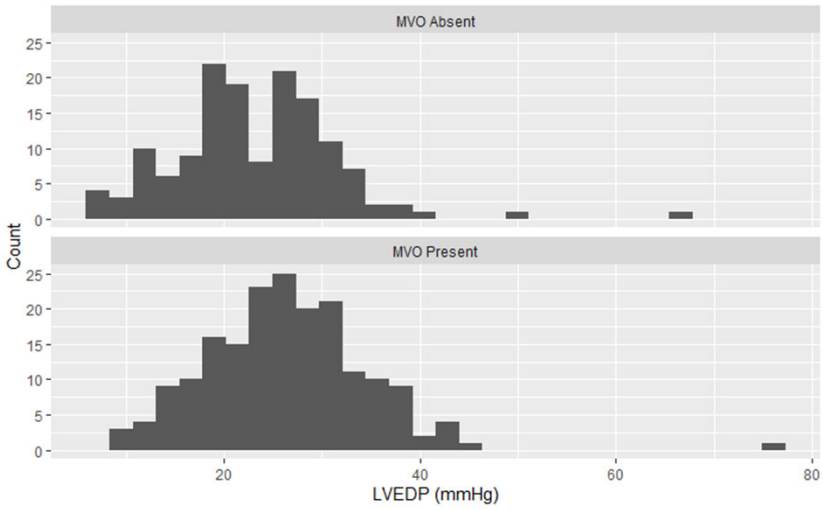


Bonfig et al., AHA 2019

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

Shah, A. MHIF 2020

MVO Remains the most important Remaining Target in STEMI!

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

Review

Optimized Treatment of ST-Elevation Myocardial Infarction

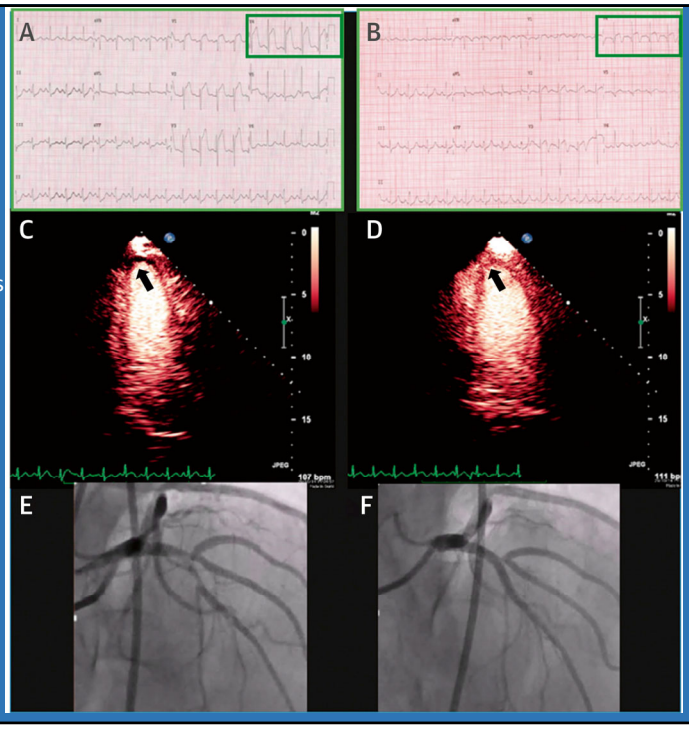
The Unmet Need to Target Coronary Microvascular Obstruction as Primary Treatment Goal to Further Improve Prognosis

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

70

Thank You !

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



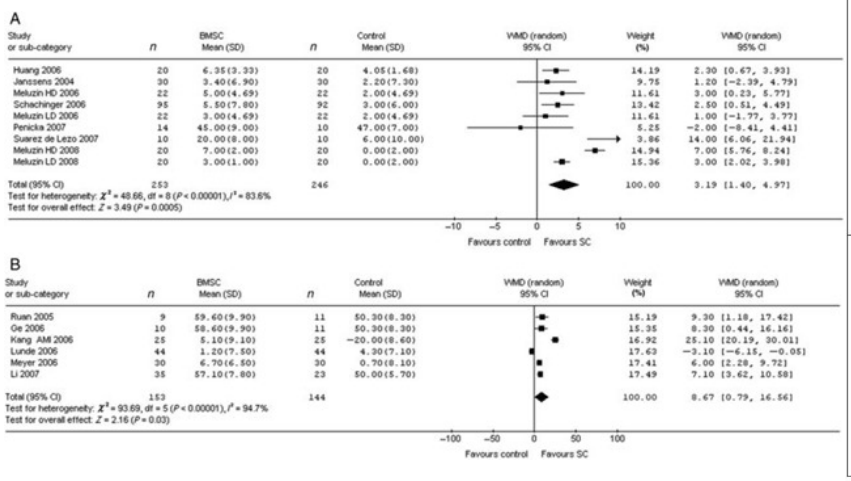
Mathias W et al. JACC 2016

CONCLUSIONS

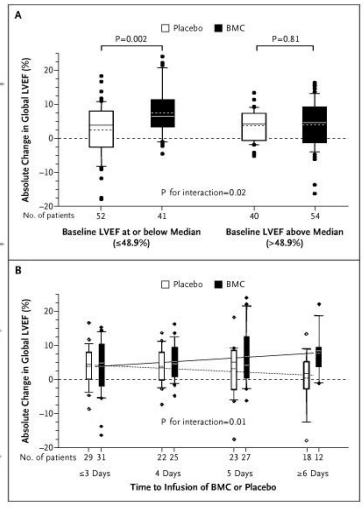
- The causes of MVO are diverse as is it's time course.
  ? Treatment Options

- 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

European Heart Journal (2011) 32, 1748–1757
doi:10.1093/eurheartj/ehq455

CLINICAL RESEARCH
Stem cells

Intracoronary autologous mononucleated bone marrow cell infusion for acute myocardial infarction: results of the randomized multicenter BONAMI trial

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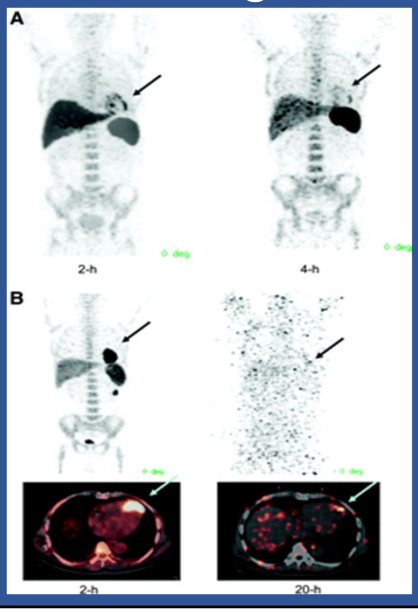
CLINICAL RESEARCH
Stem cells

Intracoronary autologous mononucleated

18F-FDG Imaging (PET) of Stem Cell Retention in Human Heart Following STEMI

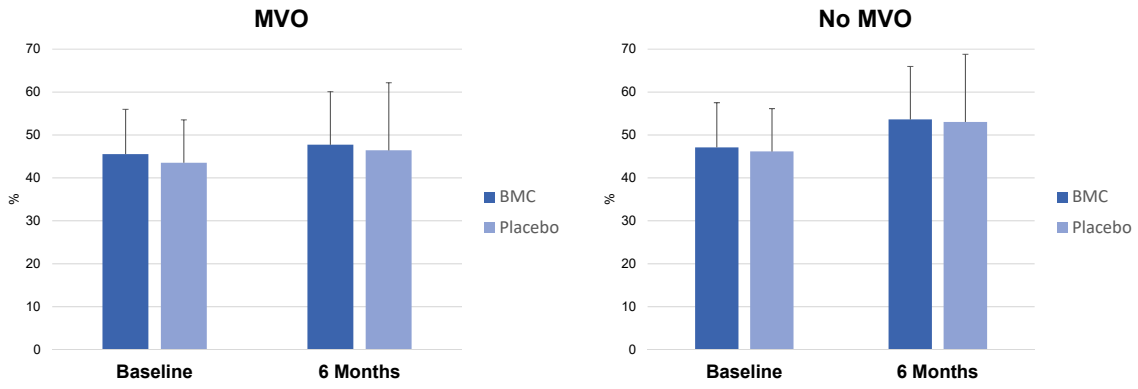
Activity of injected stem cells (%)
(10-40 million Peripheral MNCs by IC Injection)

Organ	2 h	4 h
Myocardium.	1.12	1.1
Liver	23.6	19.3
Spleen	12.3	12.8



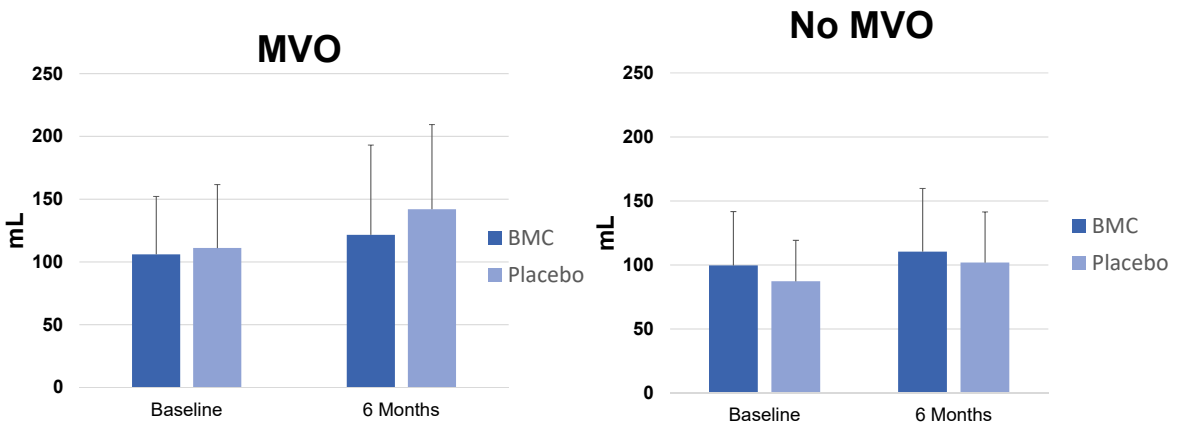
Kang WJ et al. J Nuc Med 2006

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



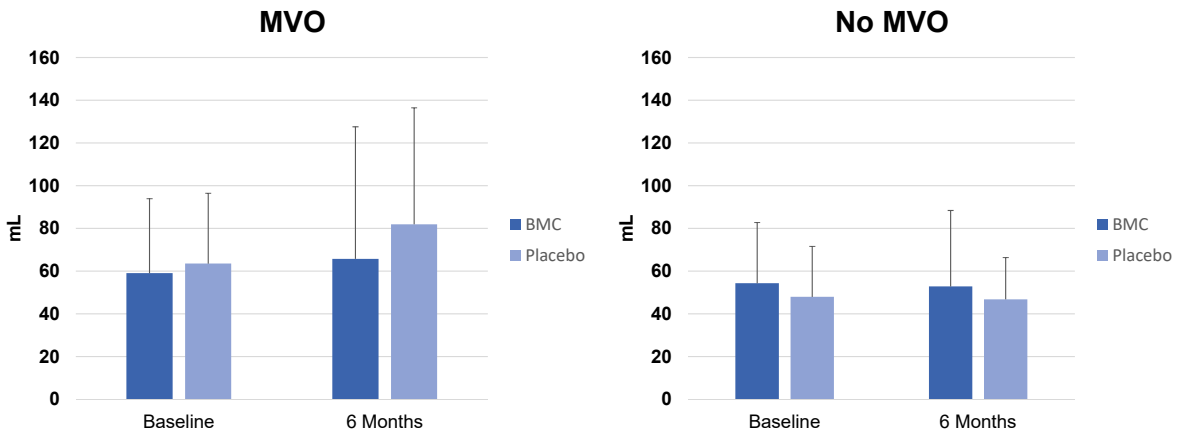
Davidson S, et al. AHA 2018 Scientific Sessions

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



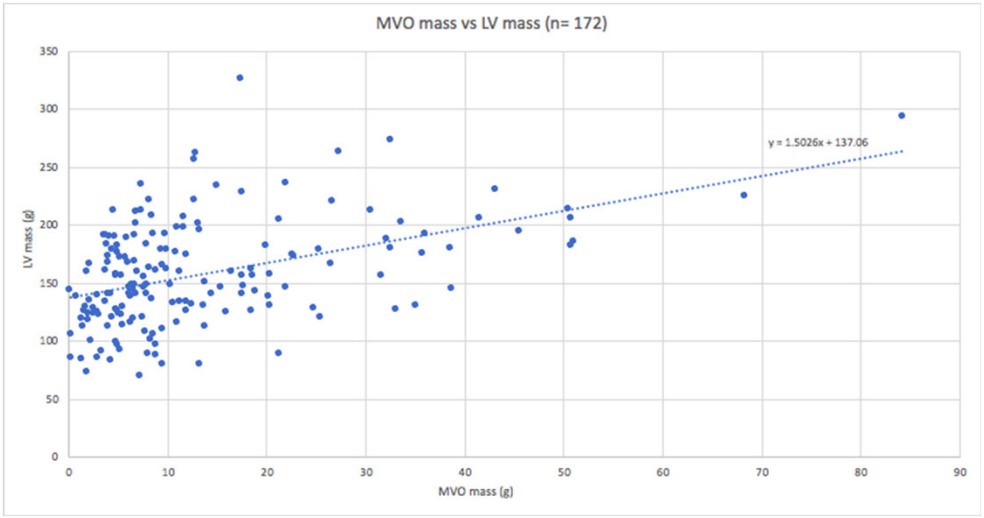
Davidson S, et al. AHA 2018 Scientific Sessions

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



Davidson S, et al. AHA 2018 Scientific Sessions

MVO mass increases with LV mass



LV mass (g)

MVO mass (g)

Bonfig N, et al. AHA Scientific Sessions 2019