1

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

Jay H Traverse, MD
Minneapolis Heart Institute Foundation
Abbott Northwestern Hospital
Associate Professor of Medicine
Cardiovascular Division
University of Minnesota School of Medicine

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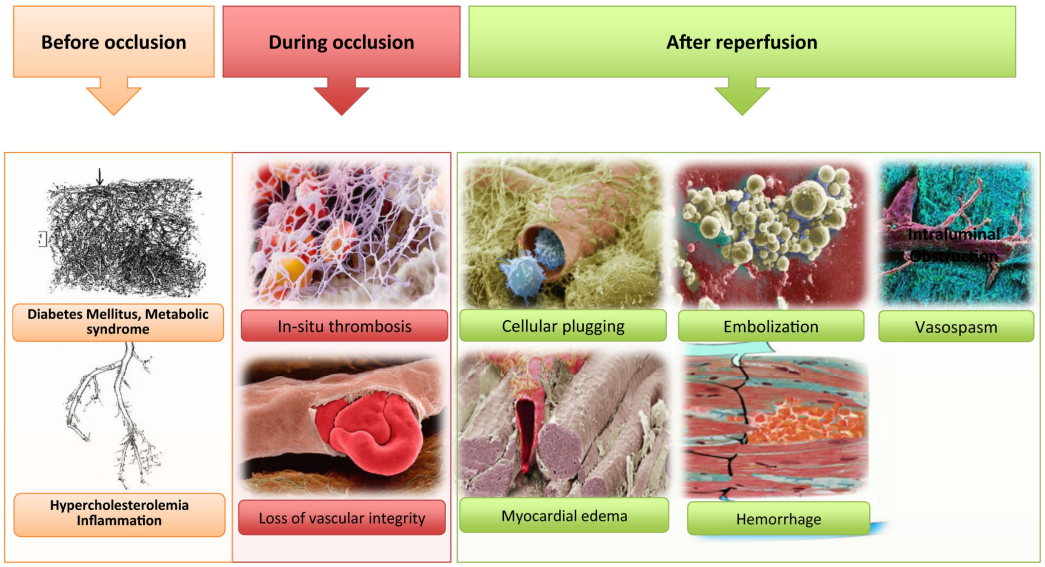
DISCLOSURES

DSMB / CEC – Abbott Vascular, BioVentrix, AltaValve

Speaker / Research – TherOx / Zoll, Boehringer-Ingelholm

3

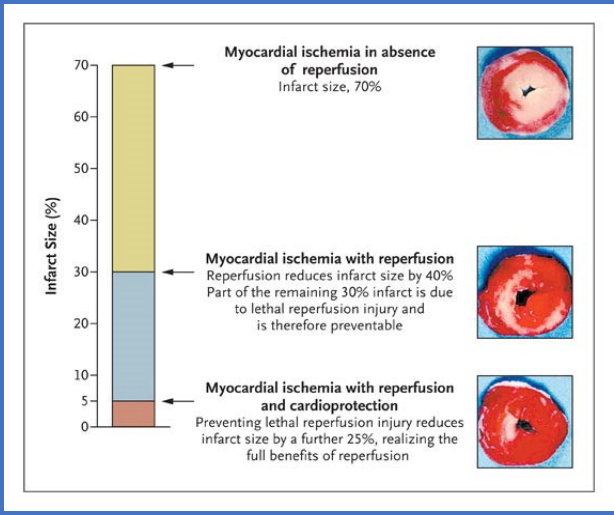
Intraluminal and Extravascular Factors of Microvascular Injury Before, During and After Reperfusion that result in MVO



Sezar et al. JAHA 2018

4

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

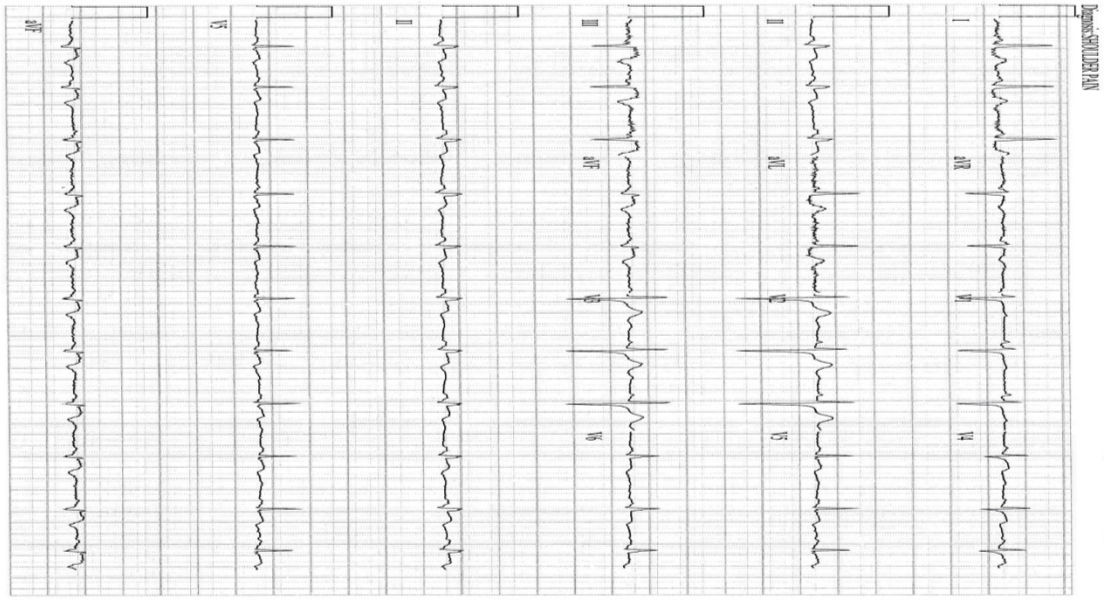


Yellon DM, Hausenloy DJ. N Engl J Med 2007;357:1121-1135.

The NEW ENGLAND JOURNAL of MEDICINE

5

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



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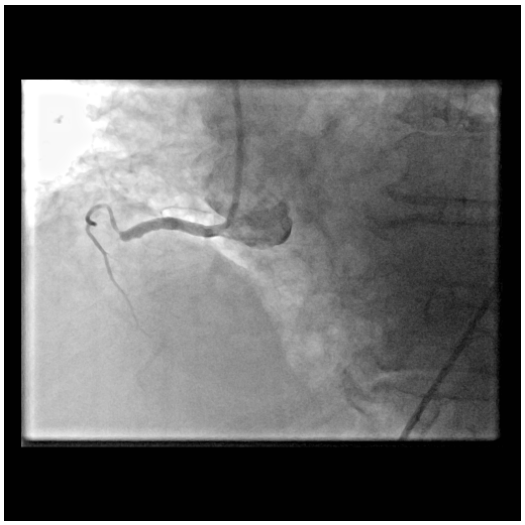
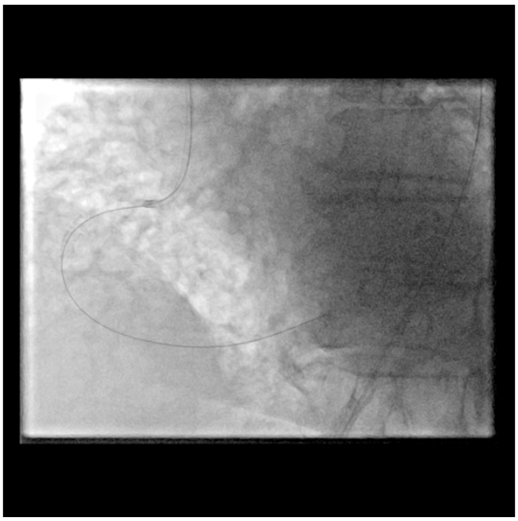
Pre- and Post-Coronary Angiogram





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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).

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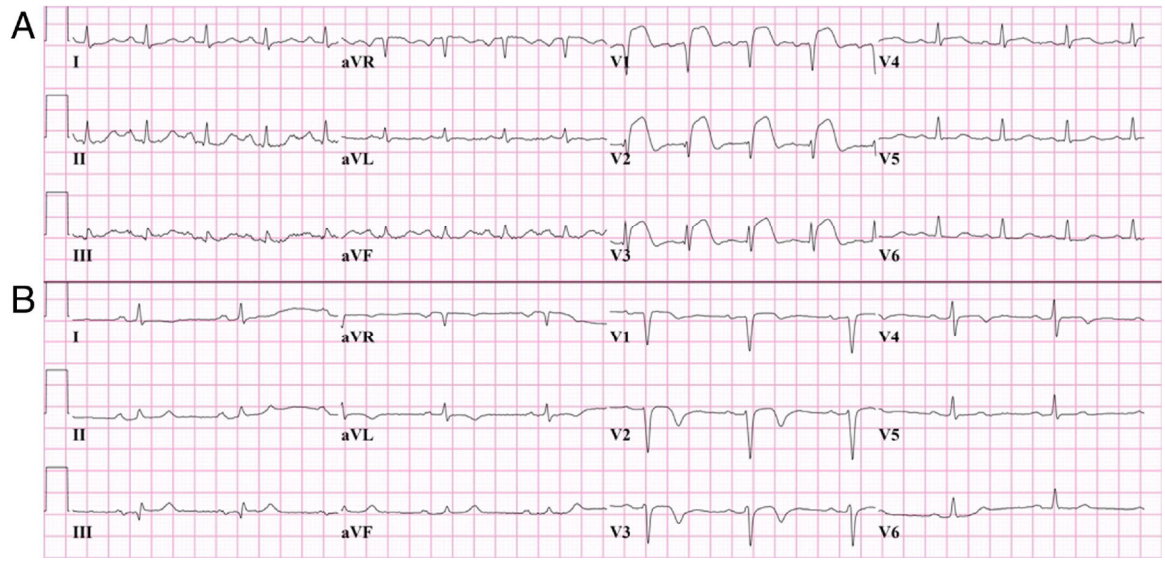

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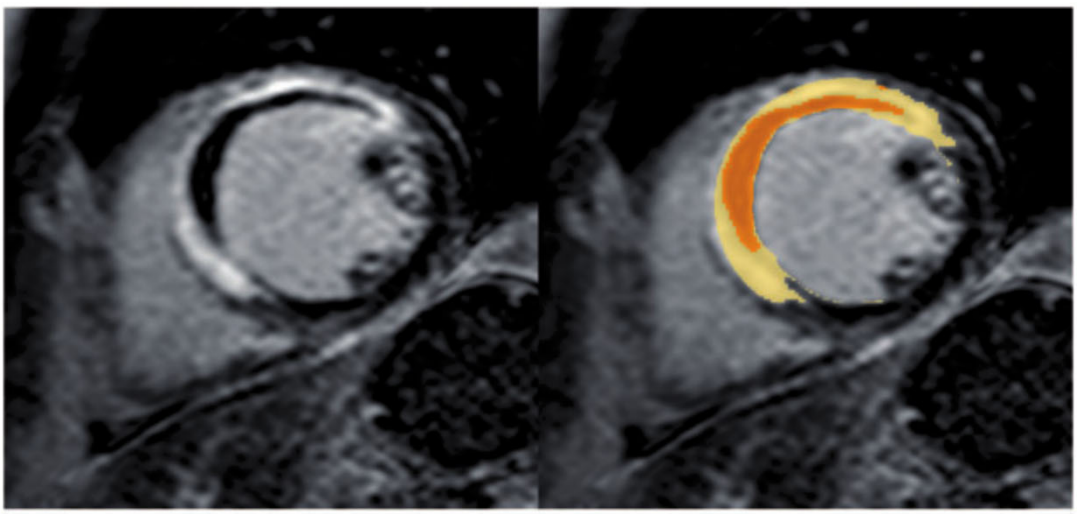
MVO is represented by hypo-enhanced (orange) region inside the hyper-enhanced (yellow) infarct region



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

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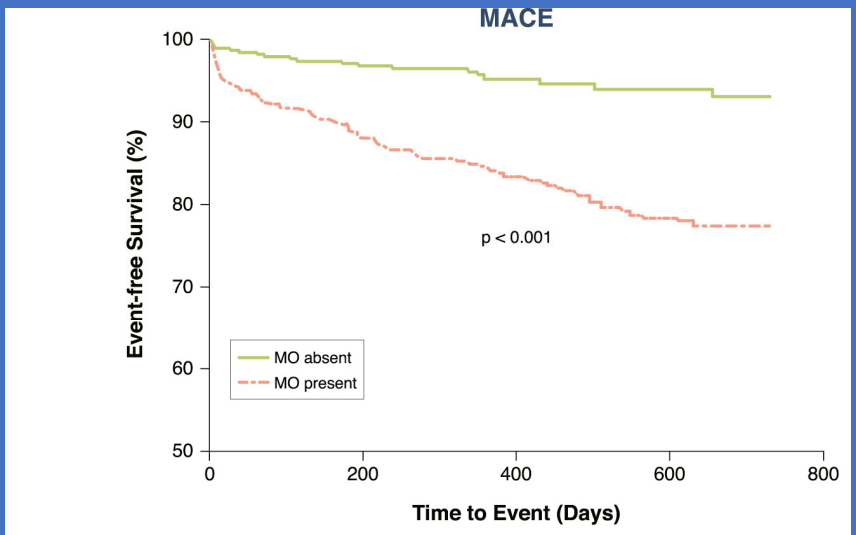
1025 STEMI Patients who received primary PCI.

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

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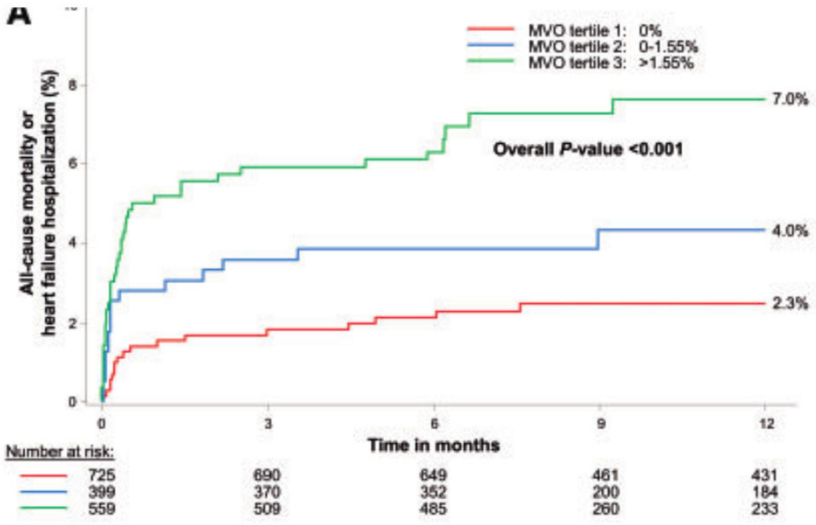
Increasing amounts of MVO are Associated with Increased All-cause Mortality and Heart Failure Admissions over 1-Year



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

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What is the Long-Term Cardiac MRI Data of Patients with MVO Following STEMI ?

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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

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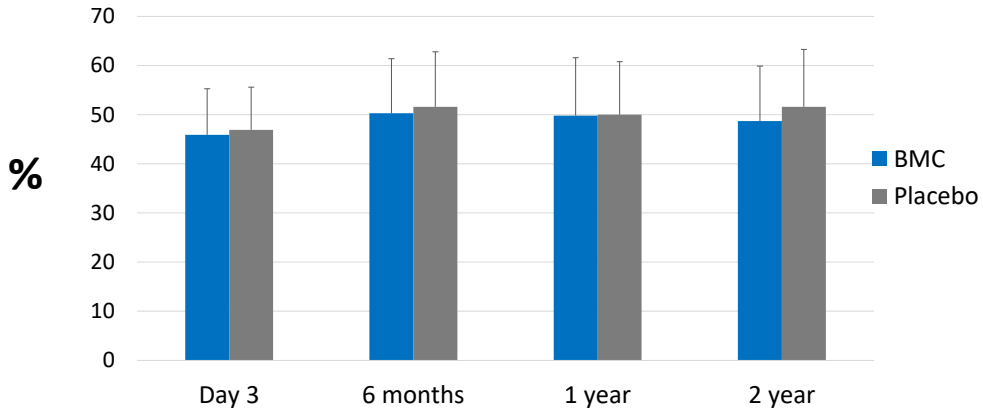
Change in LV Ejection Fraction (%) over 2 Years



Traverse J, et al. Circ Res 2018

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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

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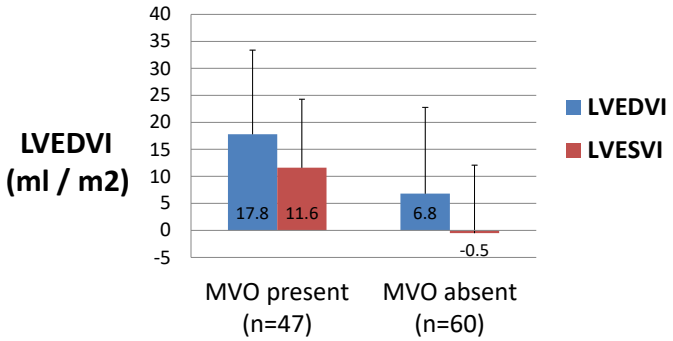
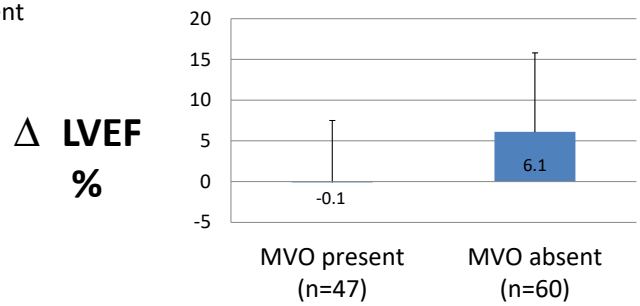
Effect of MVO on Changes in LVEF and Volumes at 6-months





Traverse J, et al. Circ Res 2018

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Clinical Investigations

Microvascular obstruction identifies a subgroup of patients who benefit from stem cell therapy following ST-elevation myocardial infarction

Sarah J. Davidson, BS[a,^,#], Jerome Roncalli, MDPhD[b,^,#], Daniel Surder, MD[c,^,#], Roberto Corti, MD[c,^,#], Atul R. Chugh, MD[d,^,#], Phillip C. Yang, MD[e,^,#], Timothy D. Henry, MD[f,^,#], Larissa Stanberry, PhD[g,^,#], Patricia Lemarchand, MDPhD[h,^,#], Jeau-Paul Beregi, MD[i,^,#], and Jay H. Traverse, MD[g,j,^,#] *Durham, NC; Zurich, Switzerland; Indianapolis, IN; Palo Alto, CA; Cincinnati, OH; Minneapolis, OH; Nantes, France; Nimes, France; Minneapolis, MN*

- 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.

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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 nterstitial and myocardial edema compressing capillaries

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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.

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Ischemia-Reperfusion Injury – The nexus between myocardial edema and MVO

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Myocardial Edema Following Reperfusion - Background

- 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.

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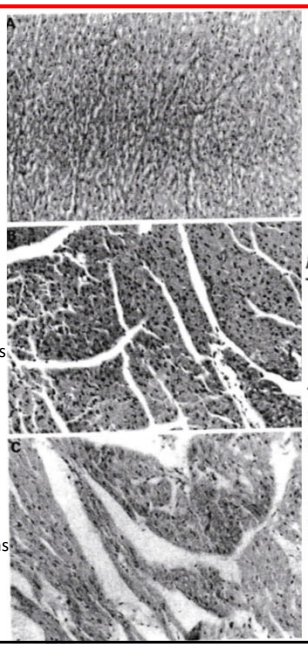
Development of Myocardial Edema is Dependent on Reperfusion



- 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

Myocardial water content and magnetic resonance imaging variables.

	Myocardial water content		T2 relaxation time		T2 weighted signal intensity		Density weighted signal intensity	
	ml·100 g^{-1} of dry tissue	Increase with respect to control myocardium	ms	Increase with respect to control myocardium	Arbitrary units	Increase with respect to control myocardium	Arbitrary units	Increase with respect to control myocardium
			Area at risk					
Non-reperfused (n=6)	427.1(8.1)*	7.1(1.3)	51.0(1.7)	3.4(4.3)	339.3(16.0)*	8.9(8.3)	1350.8(45.3)	3.0(3.3)
Reperfused (n=11)	510.7(7.9)*†	28.2(1.9)†	63.4(1.2)*†	33.1(2.1)†	478.4(9.9)*†	62.8(3.4)†	1530.8(45.7)*†	10.7(1.3)†
Without intracoronary infusion (n=4)	533.6(3.7)‡	34.8(1.3)‡	61.7(1.7)	31.5(5.5)	491.7(8.5)	59.4(8.3)	1668.5(24.4)‡	9.5(1.4)
With intracoronary infusion (n=7)	497.6(8.9)	24.4(1.7)	64.3(1.5)	34.0(1.8)	470.9(14.5)	64.7(2.8)	1420.6(18.3)	11.7(2.1)
			Control myocardium					
All hearts (n=17)	398.5(2.4)	—	48.2(0.5)	—	302.2(6.6)	—	1360.9(38.17)	—

*p<0.05 *v* control myocardium; †p<0.05 *v* area at risk in non-reperfused myocardium; ‡p<0.05 *v* reperfused myocardium with intracoronary infusion.

Garcia-Dorado et al. Cardiovasc Res 1993

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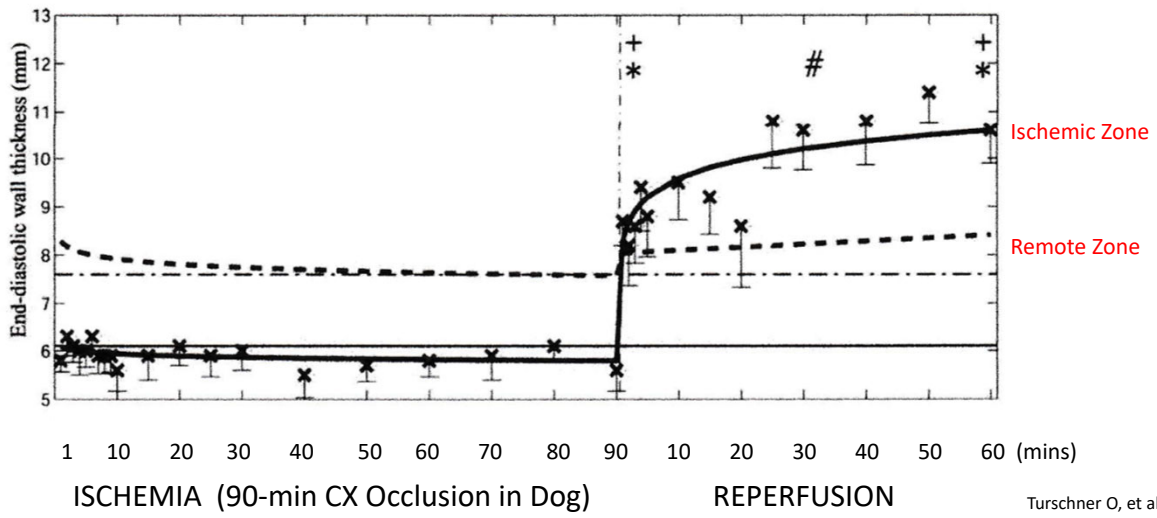
Ischemia- Reperfusion Injury Manifests as Myocardial and Interstitial Edema



Turschner O, et al. EHJ 2004

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Contents lists available at ScienceDirect
European Journal of Radiology
journal homepage: www.elsevier.com/locate/ejrad

Influence of left ventricular hypertrophy on infarct size and left ventricular ejection fraction in ST-elevation myocardial infarction☆

Łukasz A. Małek[a,*], Mateusz Śpiewak[b], Mariusz Kłopotowski[a], Joanna Petryka[b], Łukasz Mazurkiewicz[b], Mariusz Kruk[b], Cezary Kępka[b], Jolanta Miśko[c], Witold Ruzyłło[d], Adam Witkowski[a]

Clinical Research in Cardiology (2018) 107:1013–1020
https://doi.org/10.1007/s00392-018-1273-8
ORIGINAL PAPER

Impact of left ventricular hypertrophy on myocardial injury in patients with ST-segment elevation myocardial infarction

Thomas Stiermaier[1,2] · Janine Pöss[1,2] · Charlotte Eitel[1,2] · Suzanne de Waha[1,2] · Georg Fuernau[1,2] · Steffen Desch[3] · Holger Thiele[3] · Ingo Eitel[1,2]

Received: 26 February 2018 / Accepted: 7 May 2018 / Published online: 16 May 2018

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.

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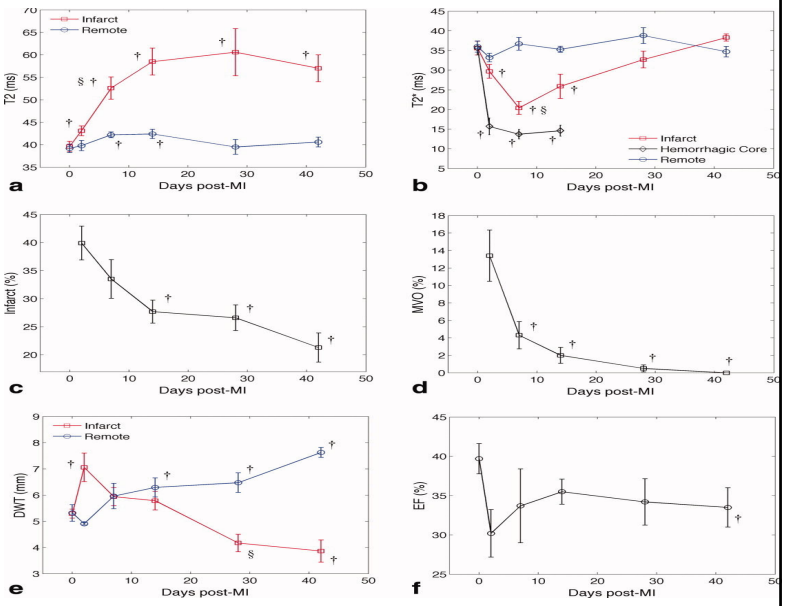
TIME COURSE of MVO, Edema, IMH and INFARCT SIZE

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

Edema

SCAR SIZE (%)



Ghugre NR, et al. Mag Res Med 2011

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- 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).

Ghugre NR, et al. Mag Res Med 2011

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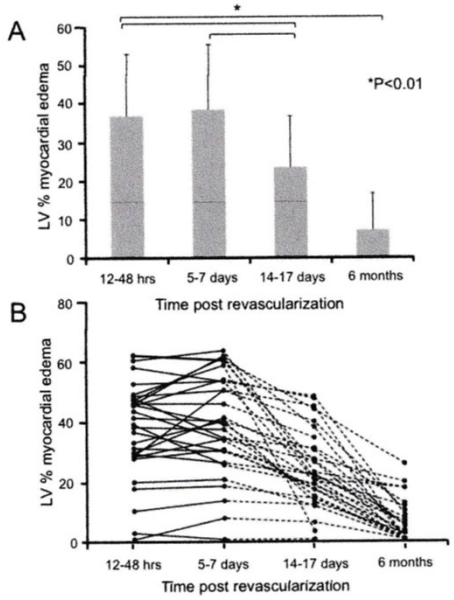
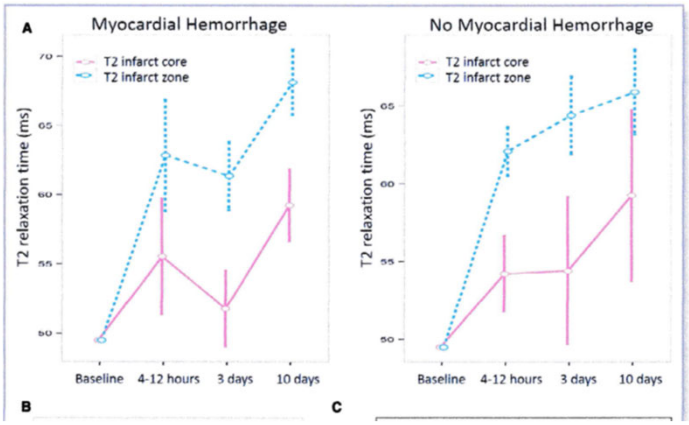
TIME-COURSE of MYOCARDIAL EDEMA in HUMANS FOLLOWING STEMI





Dall'Armellina et al. Circ Cardiovasc Img 2011

Carick D, et al. JAHA 2016

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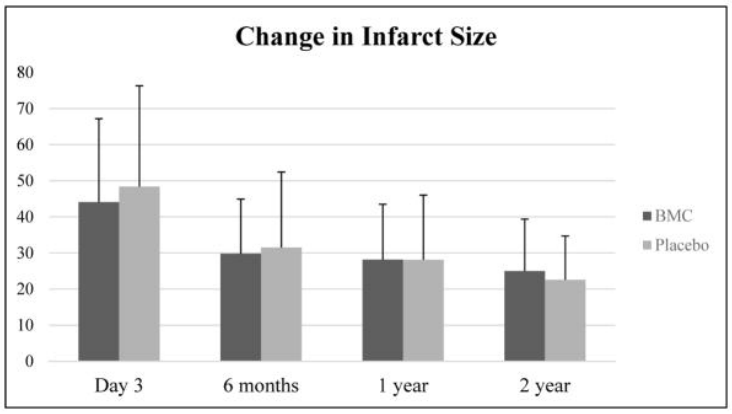
Change in LV mass and Infarct Size over 2 Years



LV Mass (g).		BMC						Placebo					
Baseline	56	179.2	48.8				27	180.4	47.1				
6 month	56	155.1	42.2	−24.1	23.0		27	163.6	43.9	−16.8	27.0		
1 year	56	148.1	43.8	−31.0	21.8		27	153.6	45.2	−26.8	24.2		
2 years	56	143.0	38.2	−36.2	25.4	0.001	27	149.9	44.1	−30.5	21.5	0.092	0.500

Traverse JH et al. Circ Res 2018

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Am J Physiol Heart Circ Physiol 323: H818–H824, 2022.
First published September 9, 2022; doi:10.1152/ajpheart.00347.2022

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY.

RESEARCH ARTICLE

Vascular Biology and Microcirculation

Increasing myocardial edema is associated with greater microvascular obstruction in ST-segment elevation myocardial infarction

Nicole L. Bonfig,[1,4] Chase R. Soukup,[1,4] Ananya A. Shah,[1] Susan Olet,[1] Sarah J. Davidson,[2] Christian W. Schmidt,[1] Rose Peterson,[1] Timothy D. Henry,[3] and Jay H. Traverse[1,4]

[1]Minneapolis Heart Institute Foundation at Abbott Northwestern Hospital, Minneapolis, Minnesota; [2]Duke University School of Medicine, Durham, North Carolina; [3]The Christ's Hospital, Cincinnati, Ohio; and [4]Cardiovascular Division, University of Minnesota Medical School, Minneapolis, Minnesota

- 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 ln 57% of patients with STEMI.

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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.

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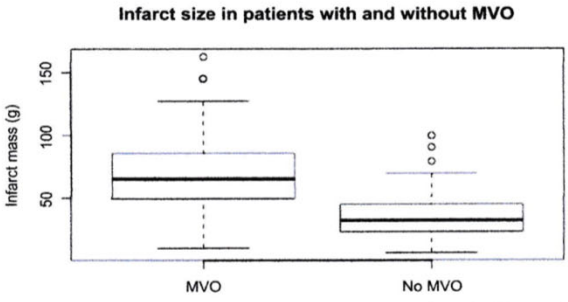

Figure 1. Box plot comparing infarct size in patients with and without microvascular obstruction (MVO). Patients with MVO had a significantly greater infarct size than patients without MVO. Data are expressed as means ± SD. $P < 0.001$.

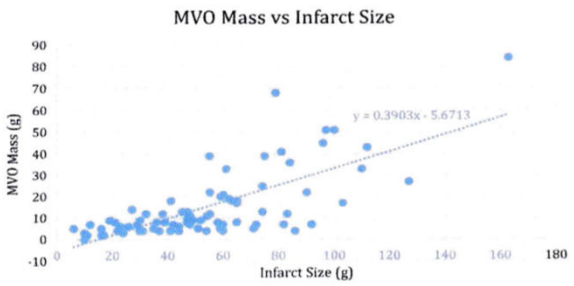

Figure 2. Plot of microvascular obstruction (MVO) mass vs. infarct size (n = 116) as measured by cardiac MRI demonstrating that MVO increases with increasing infarct size. $P < 0.001$.

- 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 < O.OO1).

Bonfig N, et al. AJP 2022

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MVO Mass Increases Linearly with LV Mass and is associated with Greater Myocardial Edema

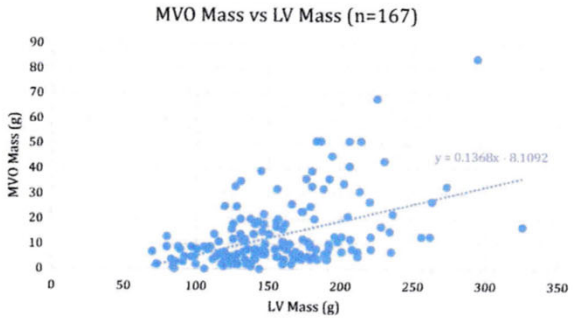

Figure 3. Plot of microvascular obstruction (MVO) mass vs. left ventricular (LV) mass (n = 167) as measured by cardiac MRI demonstrating that MVO mass increased with increasing LV mass. $P < 0.001$.

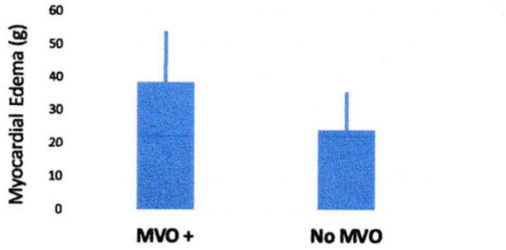

Figure 5. Myocardial edema [area at risk (AAR)] in patients with (n = 39) and without (n = 24) microvascular obstruction (MVO). AAR was significantly greater in those patients who had MVO compared with those without MVO. Data are expressed as means ± SD. $P < 0.01$.

Bonfig N, et al. AJP 2022

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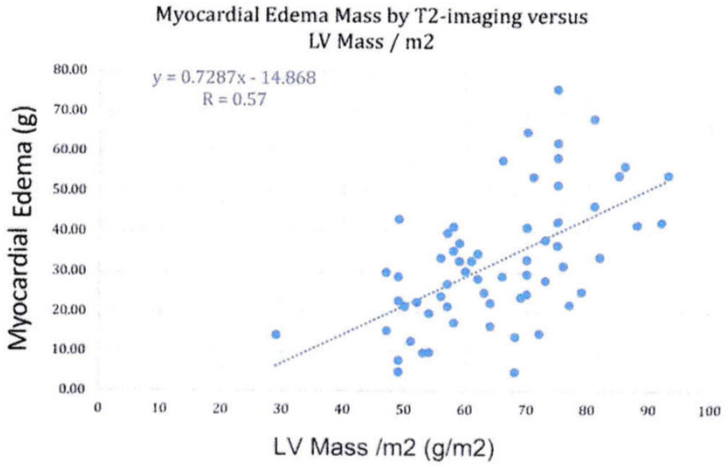

Figure 4. Plot of myocardial edema vs. left ventricular (LV) mass index (g/m^2) in a subgroup of patients that underwent T2 imaging demonstrating a strong correlation of increasing myocardial edema with increasing LV mass index (n = 63).

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

	MVO	No MVO	*P* Value
N	26	22	
LVEDP, mmHg	26 ± 8	23 ± 8	$P < 0.05$

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

Bonfig N, et al. AJP 2022

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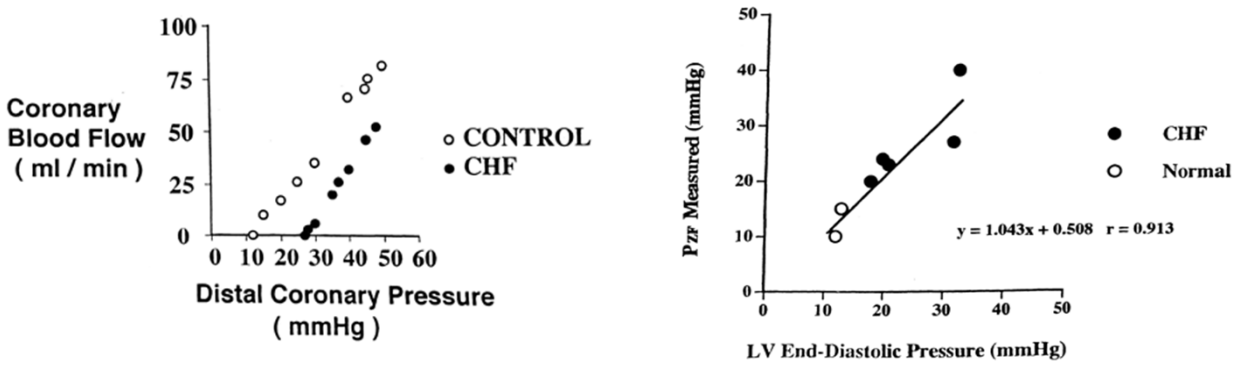
Measurement of zero-flow pressure (P_{zf}) in maximally-dilated dog heart (adenosine) under normal and elevated LVEDP (CHF) as surrogate for Extravascular Compressive Forces



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

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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 ??

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

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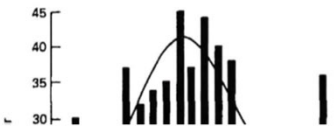
History of the triggering concept

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



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 mon
sure.[9] This increase is
echolamines upon assu
tend to increase corona
vasoconstriction could

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

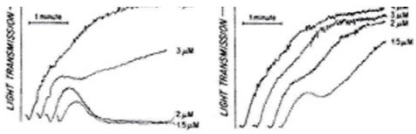
Article | Figures/Media

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
ıg 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 res
38±8 percent (P<0.02). The increase in aggregability betwe



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

ıg individual subjects was observed in the change in
ation tracings in a subject with an increase in respor

39

ors or of the American Heart Association.
From 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

sympathetic tone and circadian variation in coagulation factors.

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 mouse ischemia/reperfusion model, they demonstrated a 2.5-

occurs in humans by analyzing if the time of day onset at 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

identity. 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

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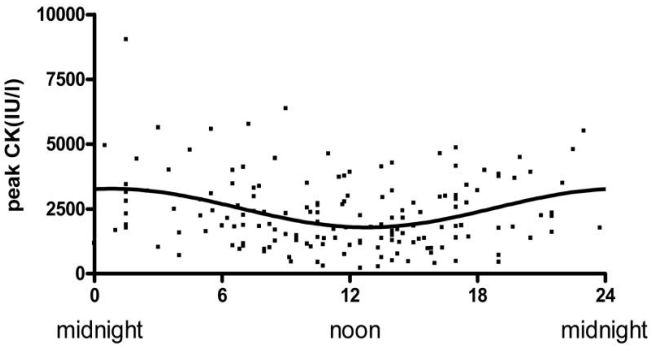

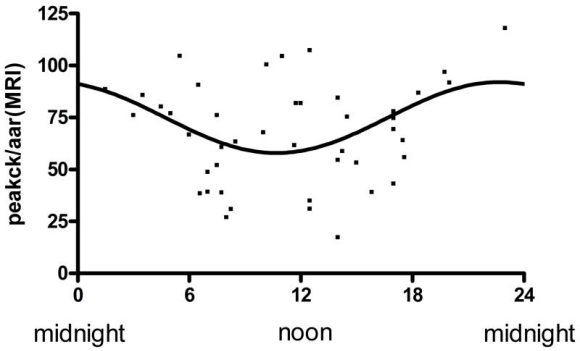

- For a given ischemic duration, myocardial injury was greatest with coronary occlusion onset around 1 AM or reperfusion around 4 AM.

Reiter et al. Circ Res 2014

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International Journal of Cardiology 366 (2022) 25–29

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journal homepage: www.elsevier.com/locate/ijcard

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

Nicole L. Bonfig [a,c], Chase R. Soukup [a,c], Ananya A. Shah [a], Sarah J. Davidson [a,b], Larissa I. Stanberry [a], Brynn K. Okeson [a], Jay H. Traverse [a,c,*]

[a] Minneapolis Heart Institute Foundation at Abbott Northwestern Hospital, Minneapolis, MN, United States of America
[b] Duke University School of Medicine, 920 East 28th Street; Suite 300; Minneapolis, MN 55407, United States of America
[c] The University of Minnesota Medical School, Cardiovascular Division, Minneapolis, MN, United States of America

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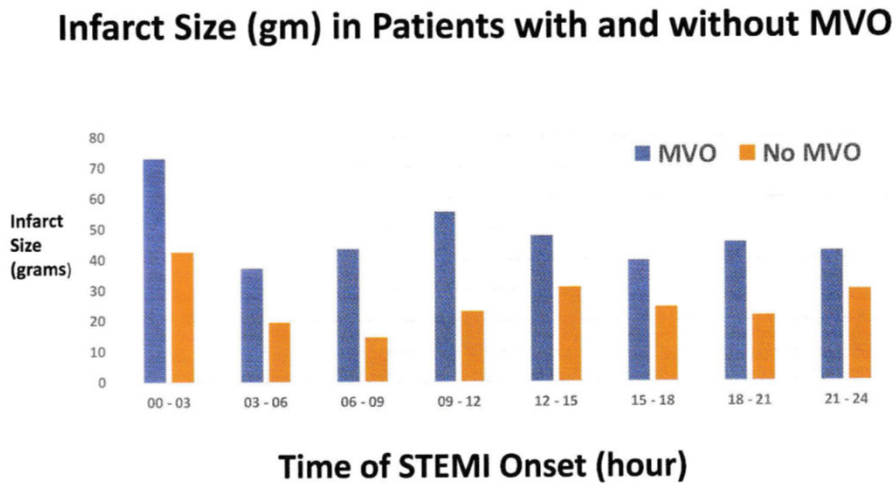

Fig. 1. Infarct size measured in grams with and without the presence of MVO over a 24-h period.

Bonfig et al. Int J Cardiol 2022

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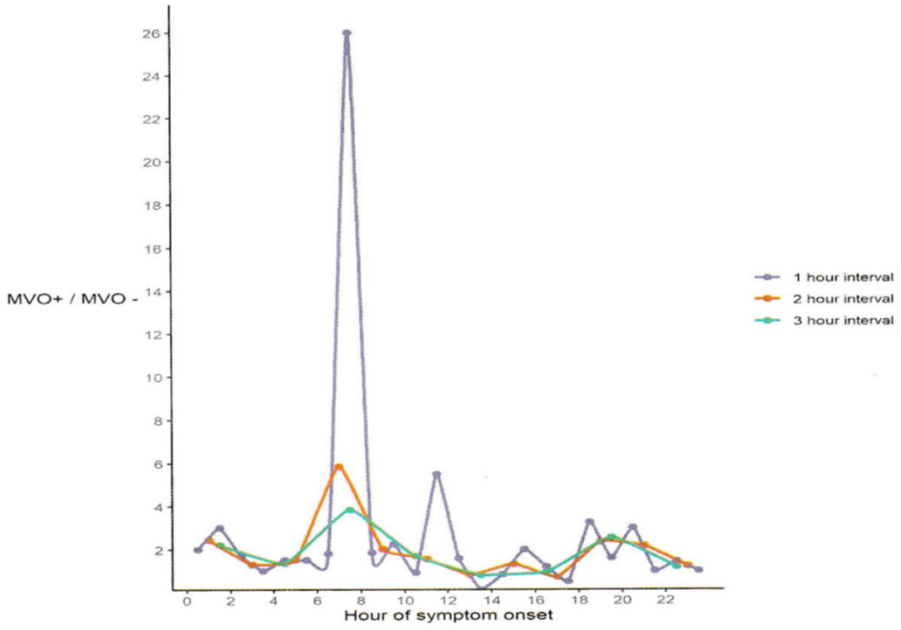
Occurrence of MVO Following STEMI is Circadian-Dependent



Bonfig Int J Cardiol 2022

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"Out of this World" Revelations About Infarct Size Following STEMI !

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Prevailing Dogma about Infarct Size

" The infarct is largely completed after 6 hours of ischemia" ?

46

The Pre-Clinical Case for Administration of SSO2 Following PCI of Late Presenters

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

International Journal of Cardiology 113 (2006) 371 – 375

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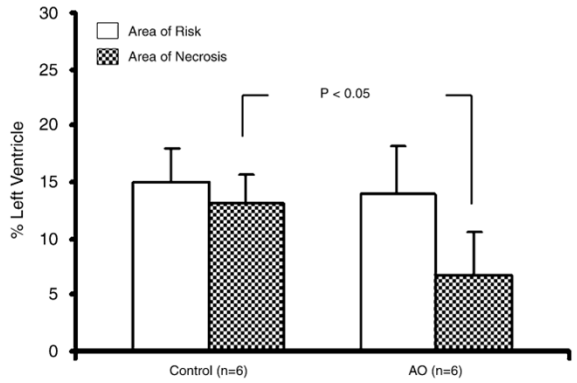
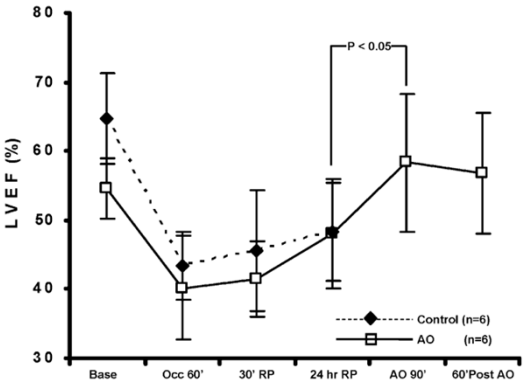
RESULTS



SSO2.



SSO2

Spears, et al. International Journal of Cardiology 113 (2006) 371 – 375

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Journal of Clinical Medicine
MDPI

Editorial

Late Presenters with ST-Elevation Myocardial Infarction: A Call to Action

Leonardo De Luca [1,2,*], Francesco Antonio Veneziano [3] and Michele Karaboue [4]

- 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

J Clin Med 2022; 11 5169

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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

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LVEF Follow-up

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

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What's Worse than MVO ?

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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.

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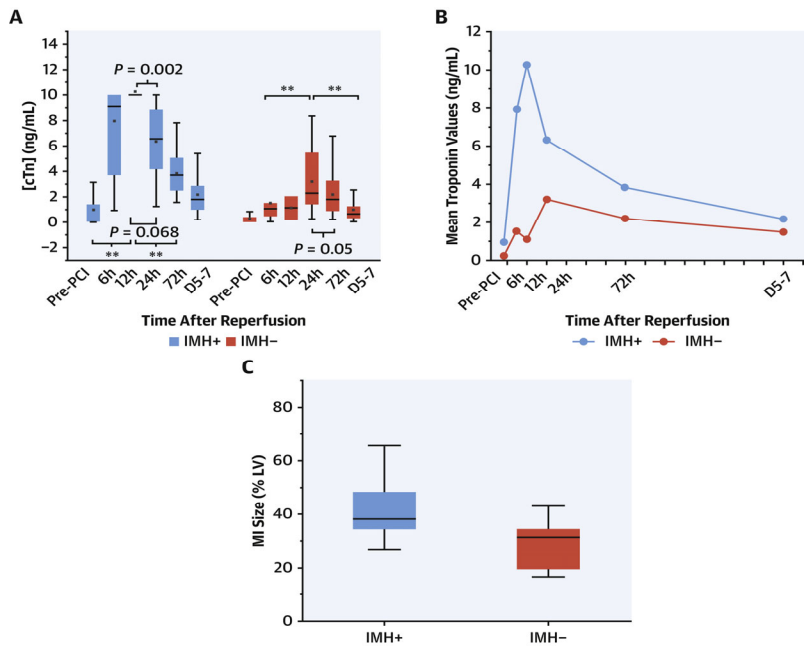

Troponin kinetics and Infarct size in STEMI patients with (n=45) and without IMH (n=19) following PCI.

Liu et al. JACC 2022

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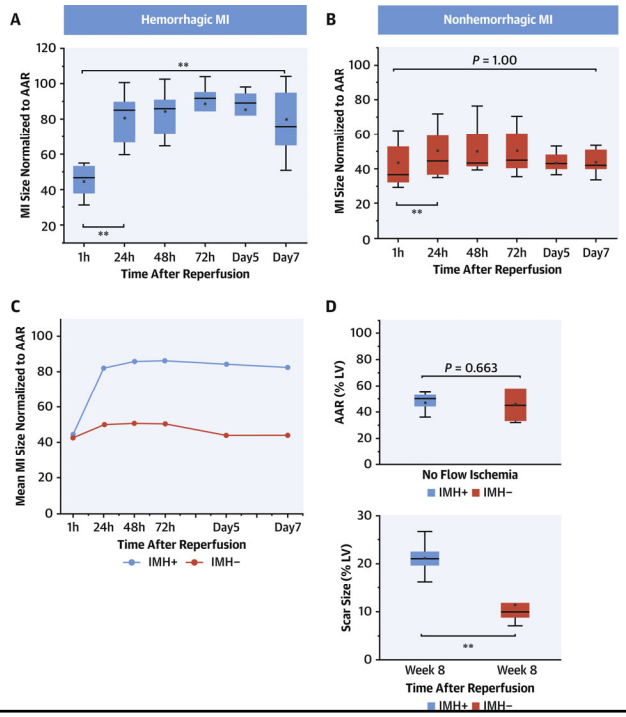

- Canines with and without IMH have similar infarct size relative to AAR at one hour post-reperfusion of 3-hr LAD coronary occlusion.
- By 24 hours, IS dramatically increases in dogs with IMH but not in dogs without IMH and loss of myocardial salvage potential. “Infarct Surge”
- Enigma! It is not known why some dogs had IMH and other dogs (humans) do not

Liu et al. JACC 2022

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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!

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

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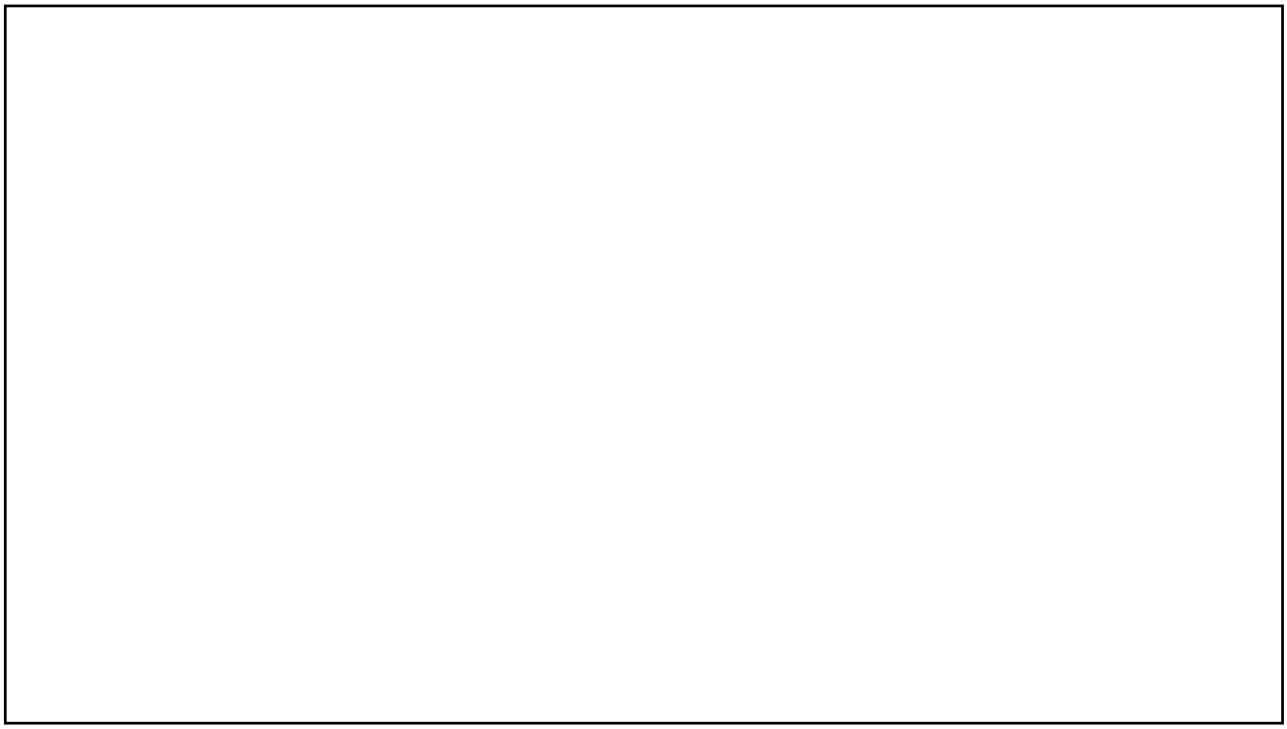

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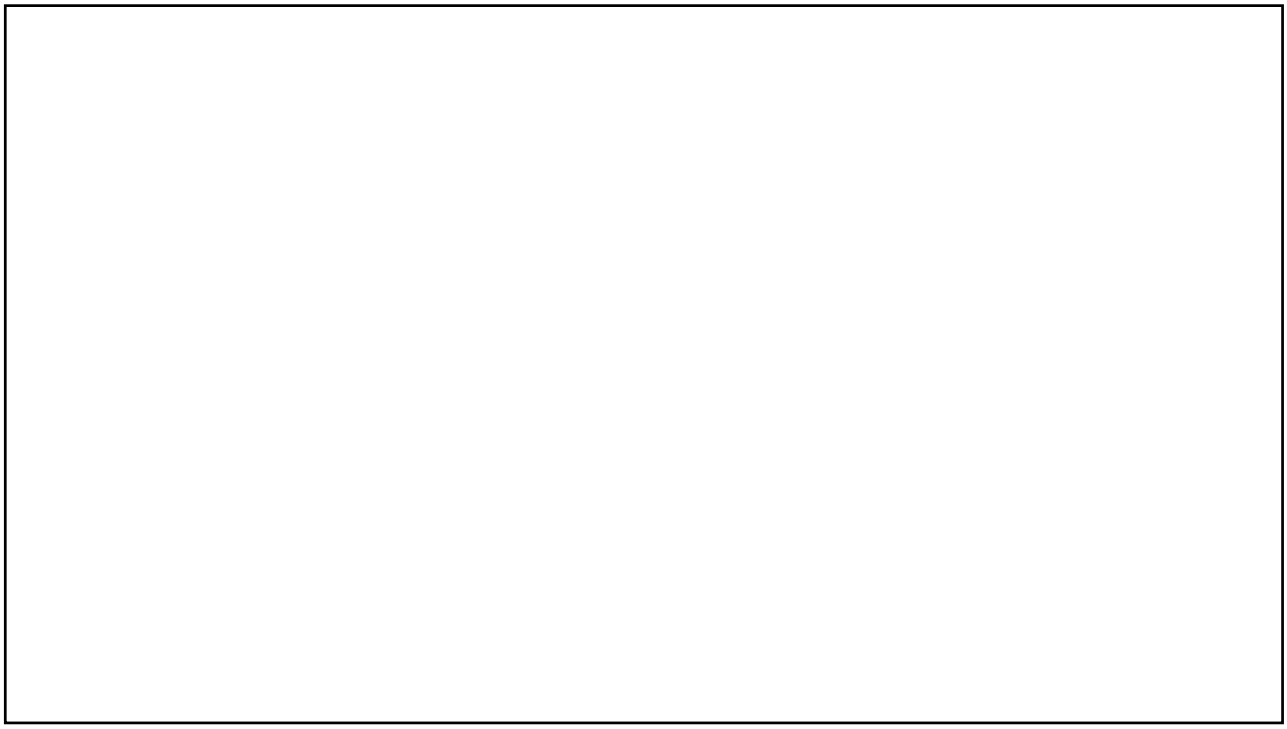

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Subjects with MVO Who Underwent Postconditioning Had less MVO as Percentage of LV mass and Infarct Size

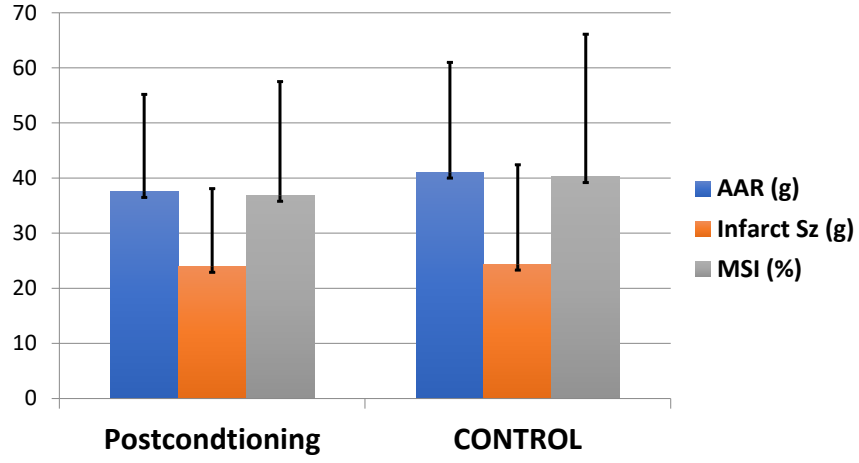
via reduced MVO may be an important, yet underreported benefit of postconditioning and may have contributed to the favorable remodeling effects we observed in this cohort. In a recent cell therapy study of similar STEMI patients,[26] we reported that subjects with MVO experienced reduced recovery

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

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

59

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

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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

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