Echocardiography as a Treatment Tool- Theranostics in Echocardiography

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Current Disclosures

Research Equipment Support: Philips Healthcare

Objectives

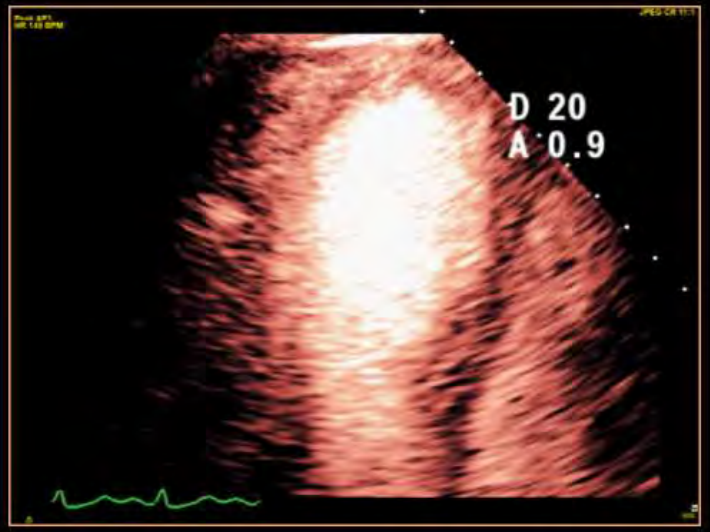
1. Present Potential Microvascular Therapeutic Applications

Dobutamine Stress Echocardiography

Apical Three Chamber View

Rest

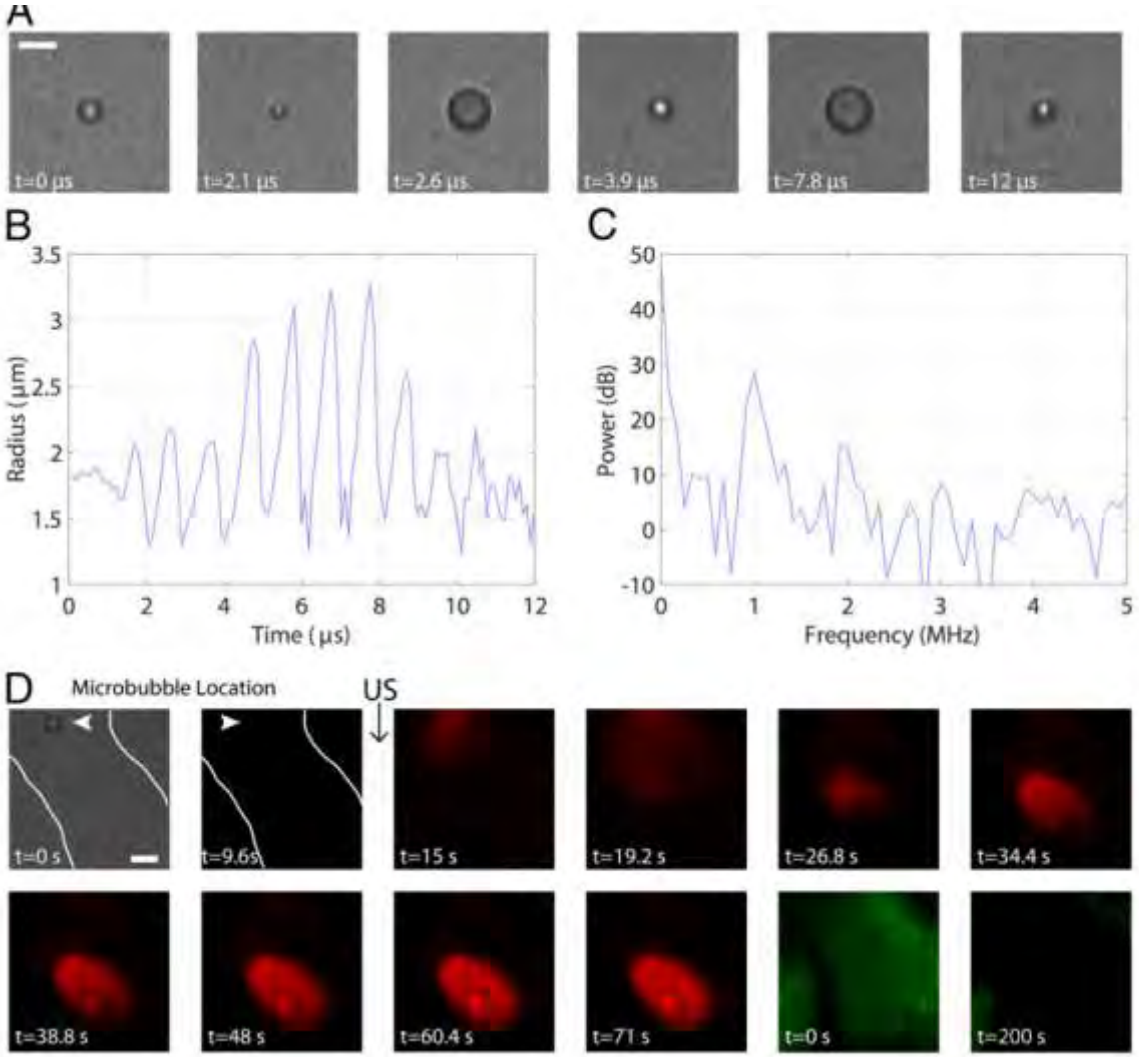
Peak



High MI Impulses

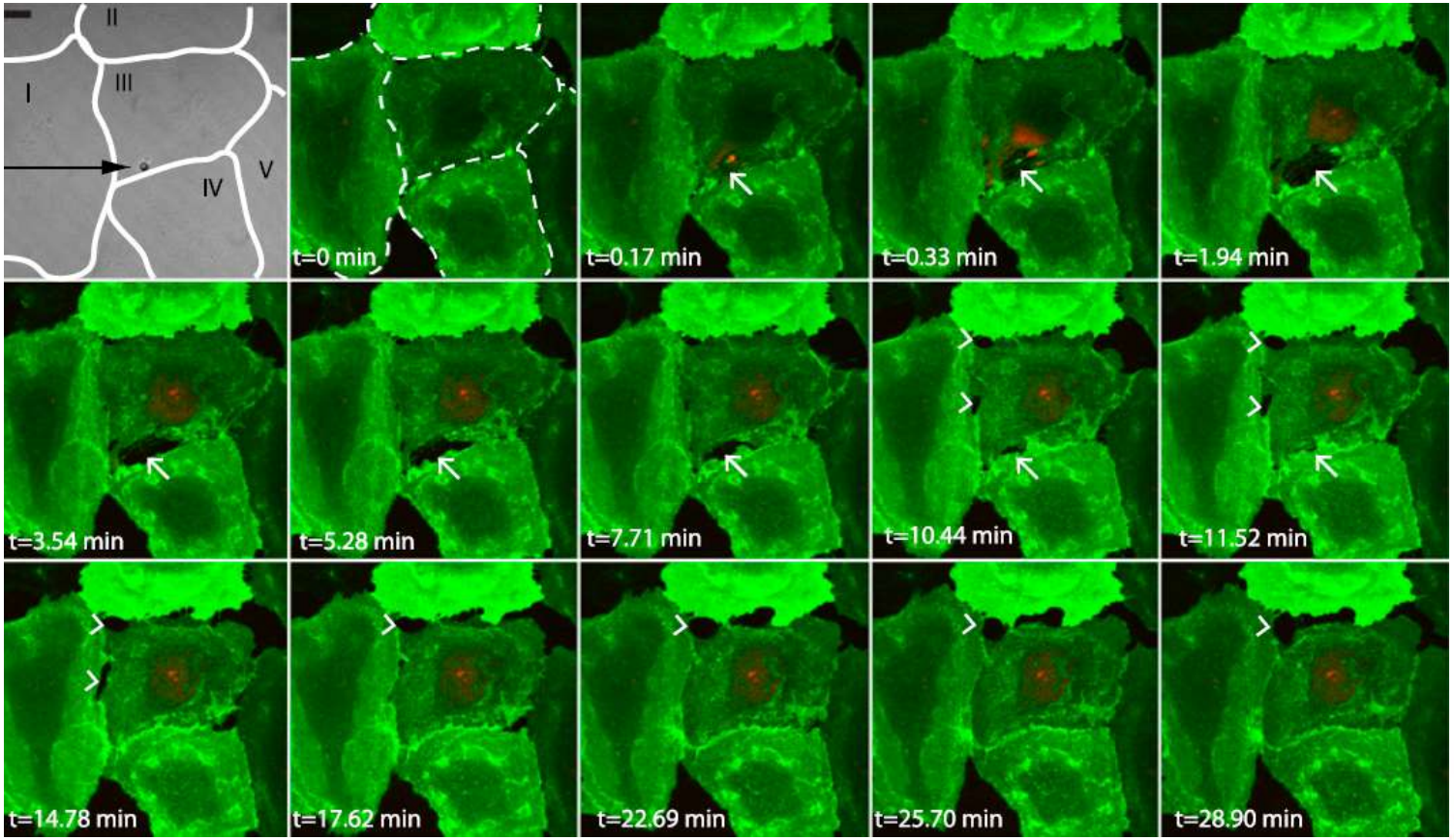
- Diagnostic for FDA Approved Indications
  - -Off Label Application: Microvascular Perfusion Imaging
- High MI impulse-Inertial Cavitation
  - Shear

The High MI Impulse in the Capillaries (8usec pulse DUS Freq)



Helfield B et.al. PNAS 2016;36:9983-9988

The High MI Impulse in the Microvasculature



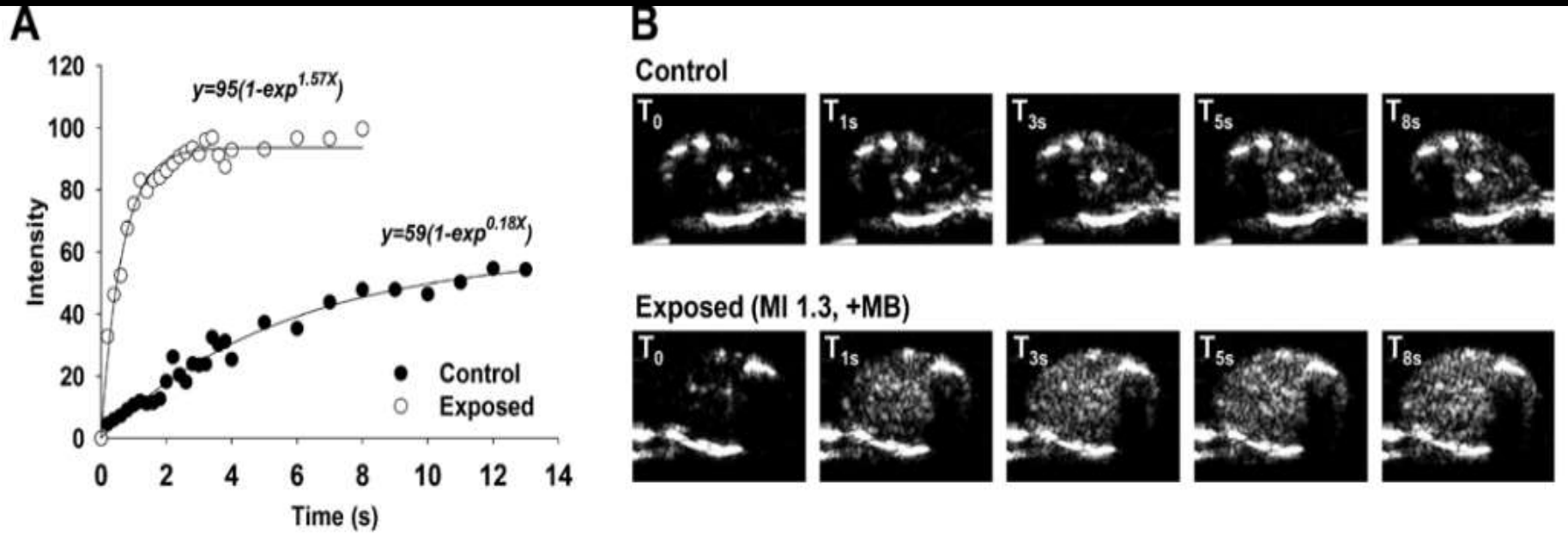
Helfield B et.al. PNAS 2016;36:9983-9988

Potential Therapeutic Effect of High MI Impulse during Microbubble Infusion

-On Cells (Endothelial/RBCs)
  Blood Brain Barrier
  Shear Dependent NO release

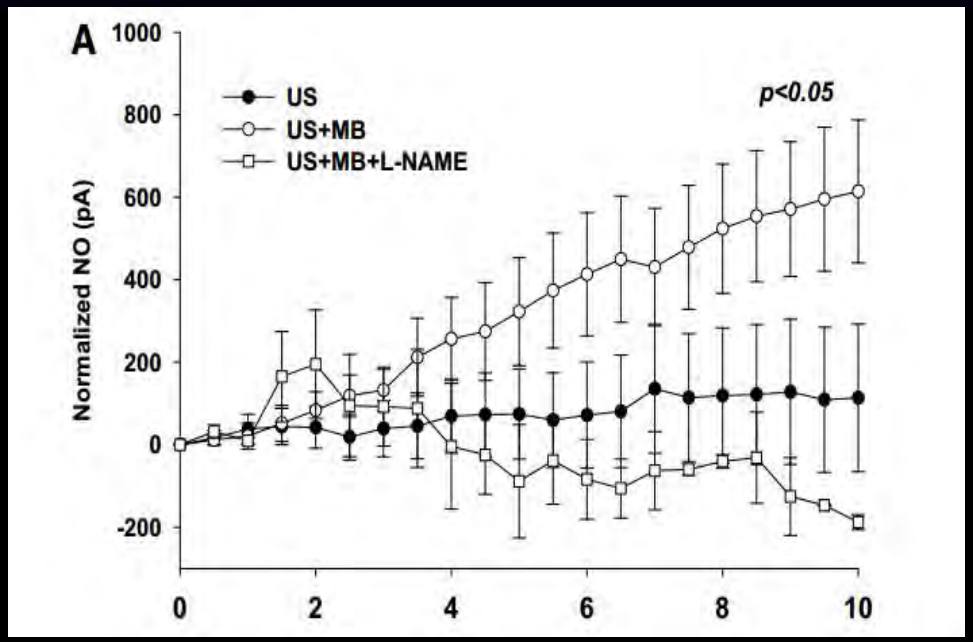
-On Thrombus-macro/micro

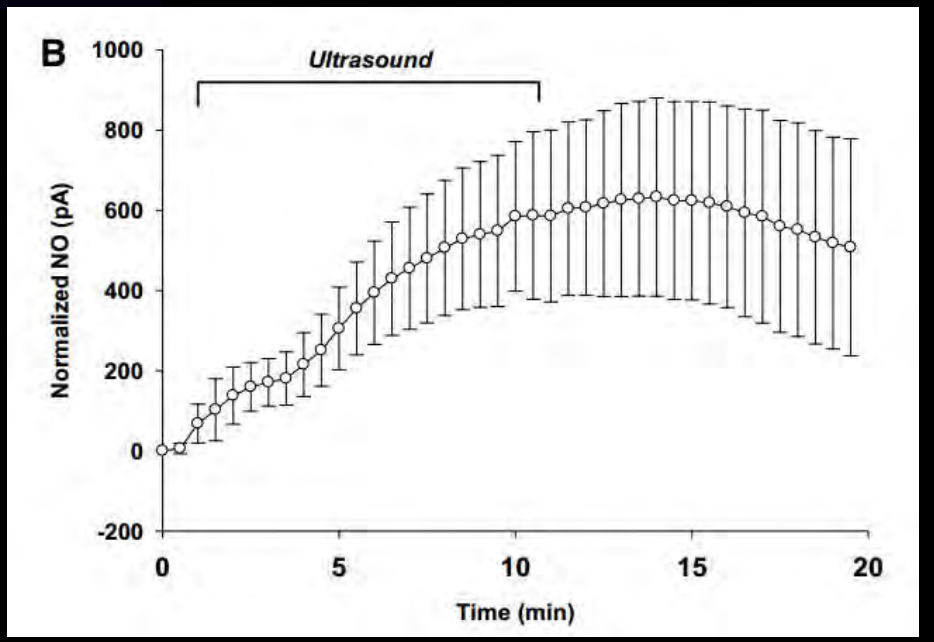
Targeted Microvascular Impulses



Belcik T et.al. Circ Cardiovasc Imaging 2015;8:e002979

Targeted Microvascular High MI Impulse





Belcik T et.al. Circ Cardiovasc Imaging 2015;8:e002979

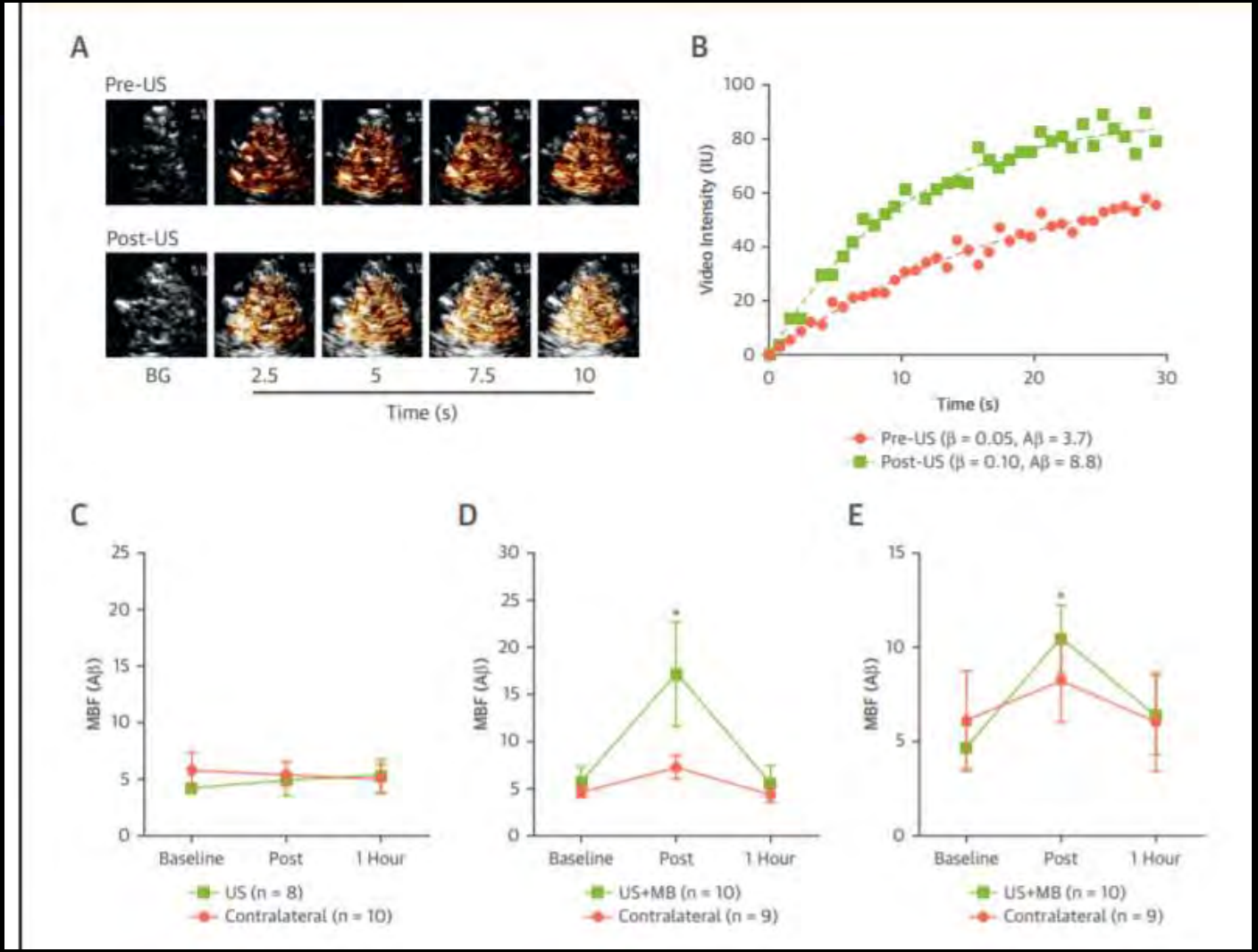
CENTRAL ILLUSTRATION: Ultrasound Exposure of the Calf Skeletal Muscle During Infusion of Ultrasound Contrast Agents Results in Microbubble Inertial Cavitation

Mason, O'N.R. et al. J Am Coll Cardiol Img. 2020;13(3):641-51.

10 patients with PVD; ABI<0.9; Symptomatic

JACC Cardiovascular Imaging

Theranostic US in PVD Patients



Mason OR et.al. J Am Coll Cardiol 2020;13:641-51

Potential Therapeutic Effect of High MI Impulse during Microbubble Infusion

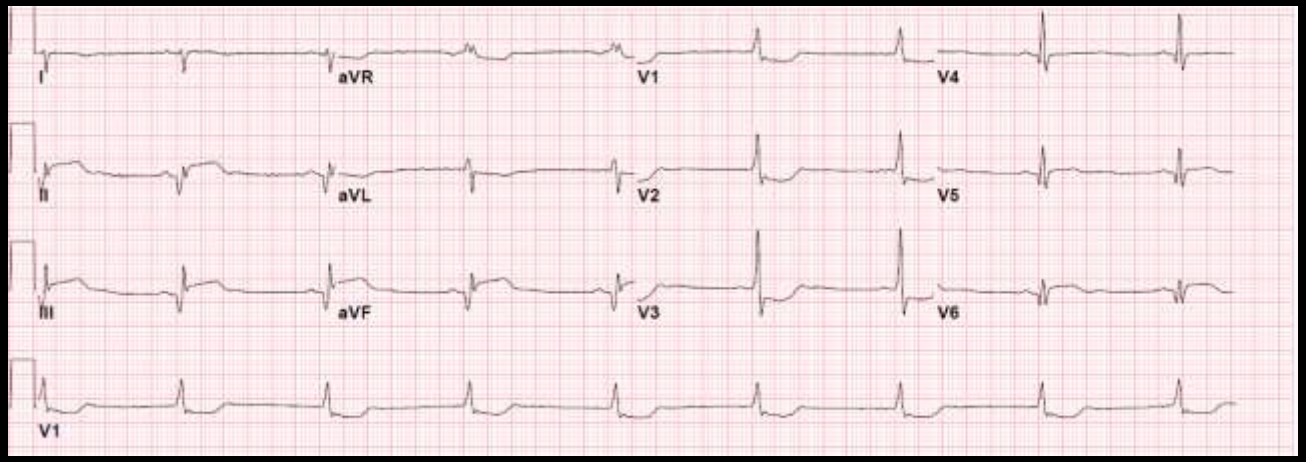
-On Cells (Endothelial/RBCs)

-On Thrombus-macro/micro

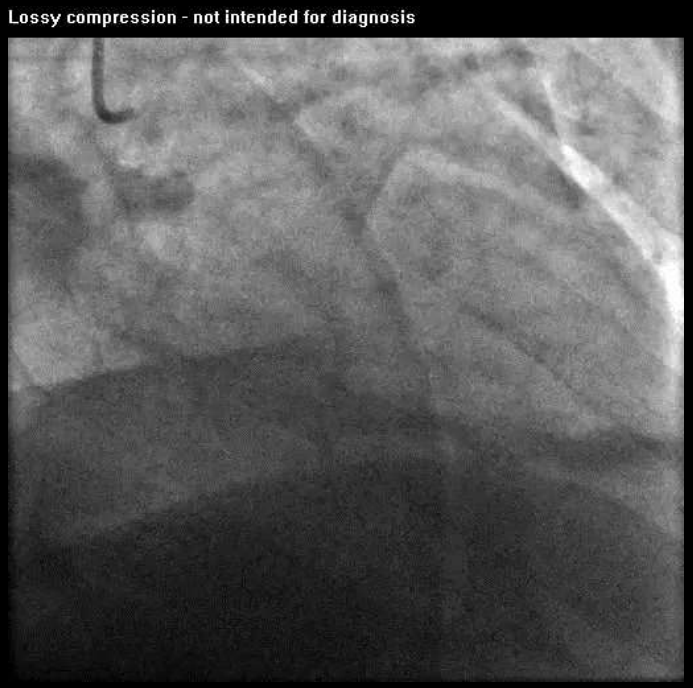
ACUTE MI

- Emergent PCI
  - Restores TIMI 2-3 flow in the Culprit Vessel
  - Almost complete pain relief
  - Microvascular Effects

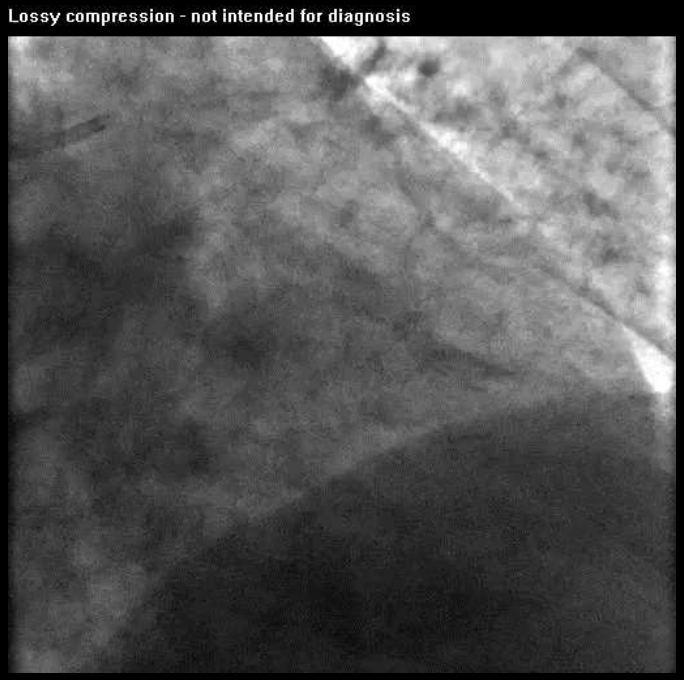
64 year old male no prior cardiac history with prolonged substernal chest pain-intermittent



Pre PCI



Post PCI-read out as TIMI 3 flow in the infarct vessel.



Post Successful Circumflex Stenting- Echo one day later……

Acute STEMI treated with TIMI 3 flow post PCI

Variable	Total (N=321)
Age(y)	64 ± 12
Male	209 (65%)
Caucasian	281 (88%)
Smoker	236 (74%)
Hypertension	166 (52%)
Hyperlipidemia	145 (45%)
Diabetes mellitus	61 (19%)
History of CAD	212 (66%)
History of CHF	39 (12%)

Xie F, Qian L et.al. Circ Cardiovasc Imaging 2020;13:e010091

Microvascular Flow Post Treated STEMI TIMI 3 FLOW

- TIMI 3 flow in the Infarct Vessel
- Normal MVP at 24-48 hours= 61 patients (19%)
- Delayed MVP at 24-48 hours=132 patients(41%)
- MVO-at 24-48 hours =128 patients (40%)

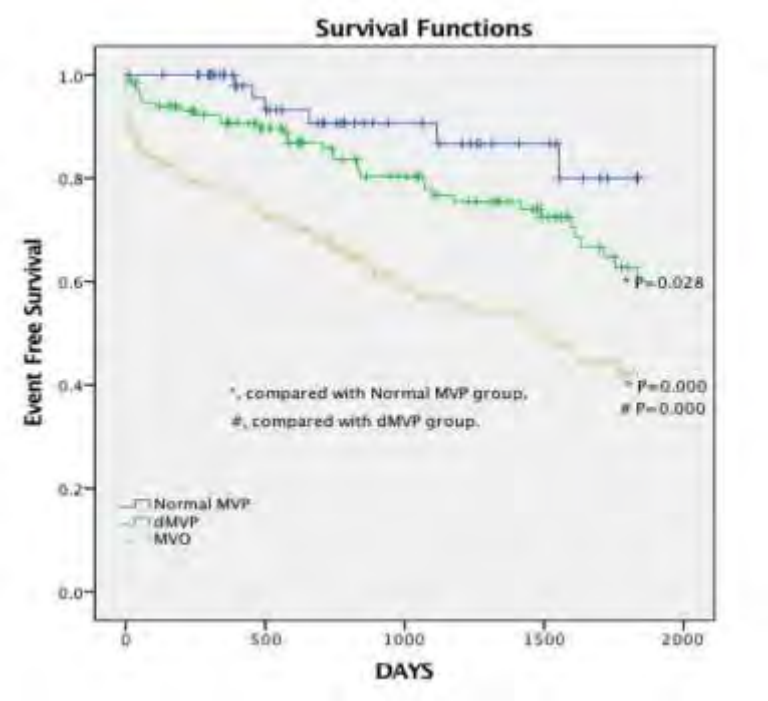
Xie F, Qian L et.al. Circ Cardiovasc Imaging 2020;13:e010091

Distribution of infarct territory

Territory	Total (N=321)	Normal MVP group (n=61 [19%])	dMVP group (n=132 [41%])	MVO group (n=128 [40%])
LCx	53 (17%)	14 (23%)	23 (17%)	16 (13%)
LAD	138(43%)	8 (13%)	43 (33%)*	87 (68%)*#
RCA	140 (40%)	40 (66%)	71 (54%)	29 (23%)*#

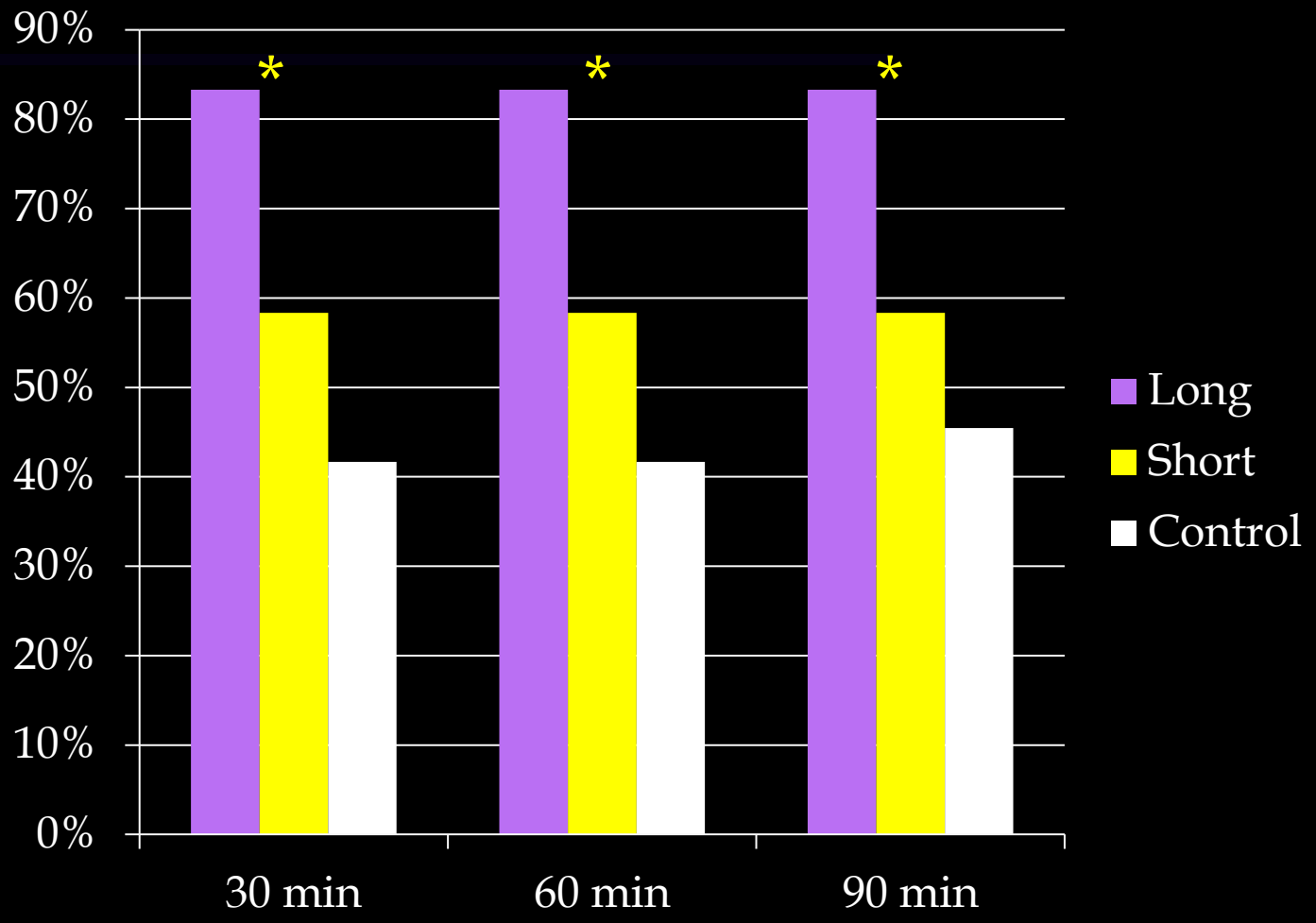
Xie F, Qian L et.al. Circ Cardiovasc Imaging 2020;13:e010091

Microvascular Obstruction with TIMI 3 Flow



Xie F, Qian L et.al. Circ Cardiovasc Imaging 2020;13:e010091

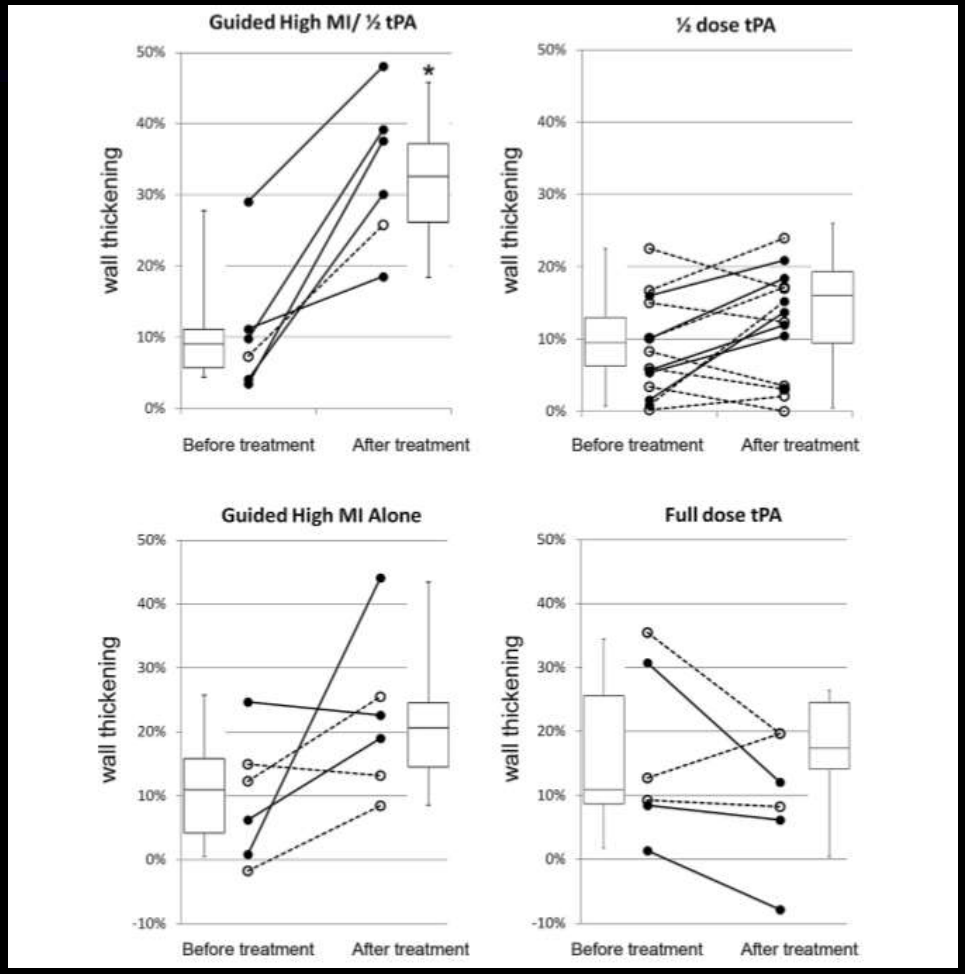
% Epicardial Recanalization Rates



Xie F et.al. Plos One 2013;8(7):e69780

*p<0.05 compared to control

Wall Thickening Improvement



Wu J et.al. Heart 2015;101:1468-74

Sonothrombolysis in ST Segment Elevation Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention: Final Results from the First Randomized Study in Humans

Wilson Mathias, Jr[1], Jeane M Tsutsui[1], Bruno G Tavares[1], Agostina Fava[2], Miguel O D Aguiar[1], Bruno C Borges[1], Mucio T Oliveira Jr[1], Alexandre Soeiro[1], Jose C Nicolau[1], Henrique B Ribeiro[1], Hsu Pochiang[1], João C N Sbano[1], Abdul Morad [2], Andrew Goldsweig[2], Carlos E Rochitte[1], Bernardo B C Lopes[1], José A F Ramirez[1], Roberto Kalil Filho[1], Thomas R Porter[2].

Research Project *# 2010/52114-1*

Final IRB Approval *# 342.799 (07/08/2013)*

Clinical Trials.gov *# NCT02410330*

[1] *Heart Institute (InCor), The University of São Paulo Medical School, Brazil*

[2] *Cardiology Department of The University of Nebraska Medical Center*

FAPESP

State of São Paulo, Government Agency "BRAZILIAN NIH"

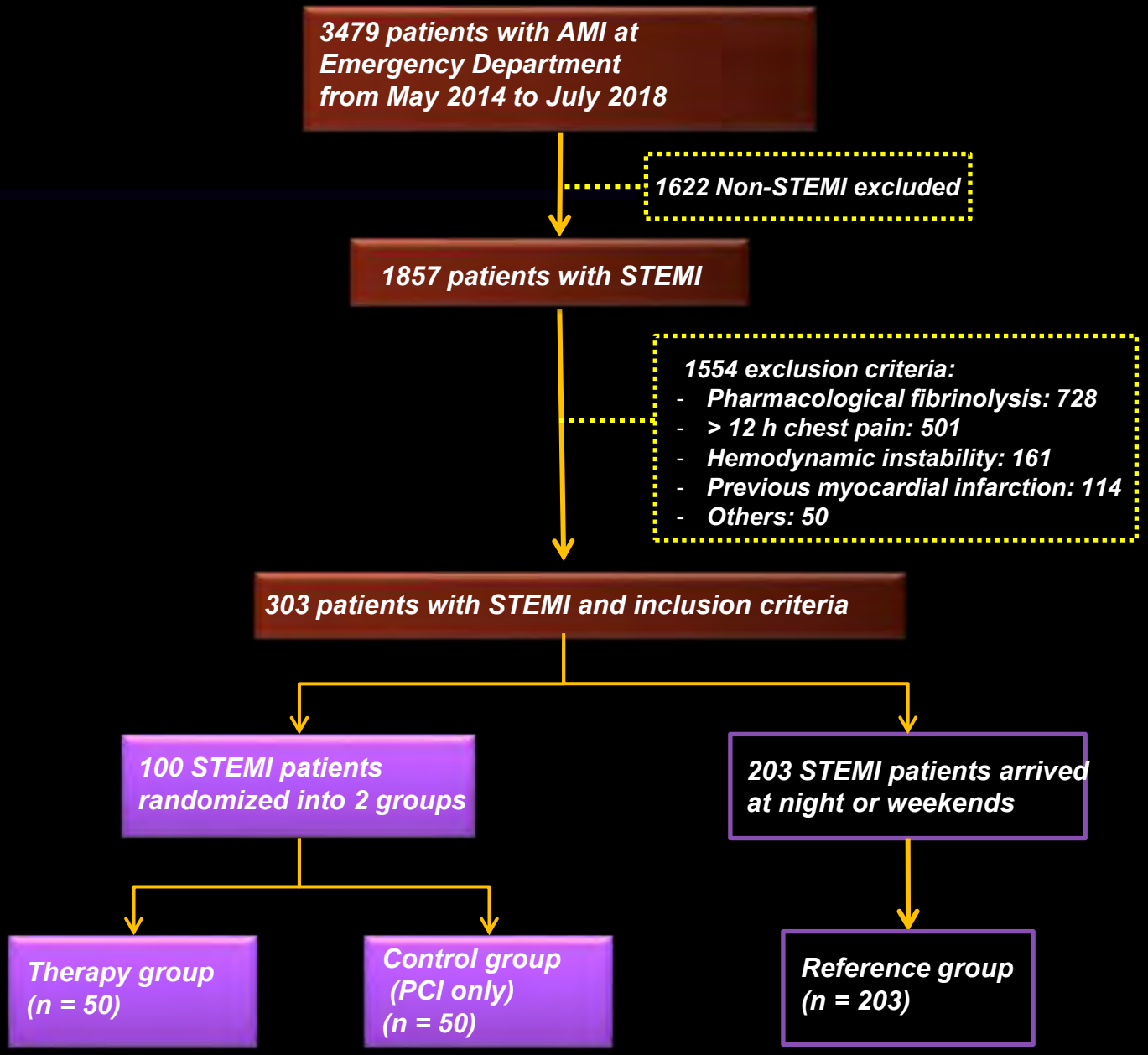
InCor HCFMUSP Ciência e Humanismo

Heart Institute (InCor)
University of São Paulo Medical School
São Paulo, Brazil

University of Nebraska Medical Center

Theodore F. and Claire M. Hubbard Family Foundation

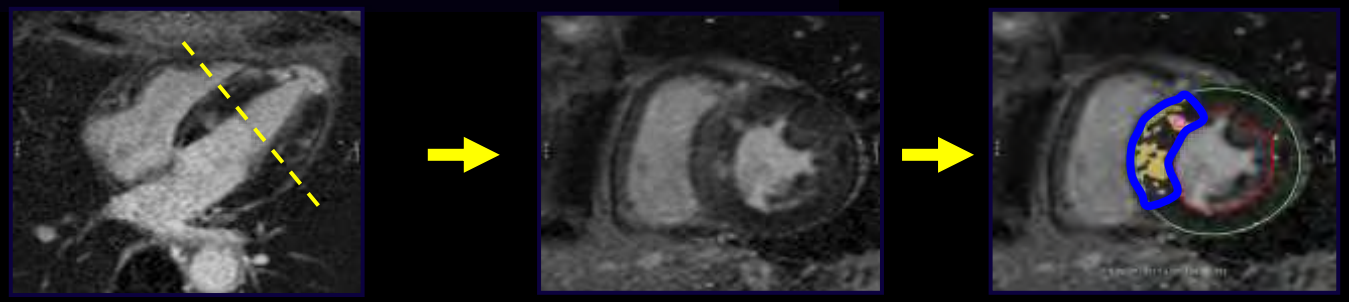
Patient Selection



Echocardiography and MRI

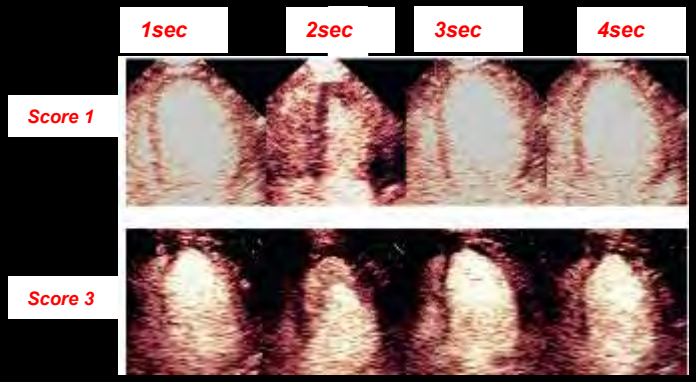
MRI by Achieva de 1,5T, Philips Medical Systems

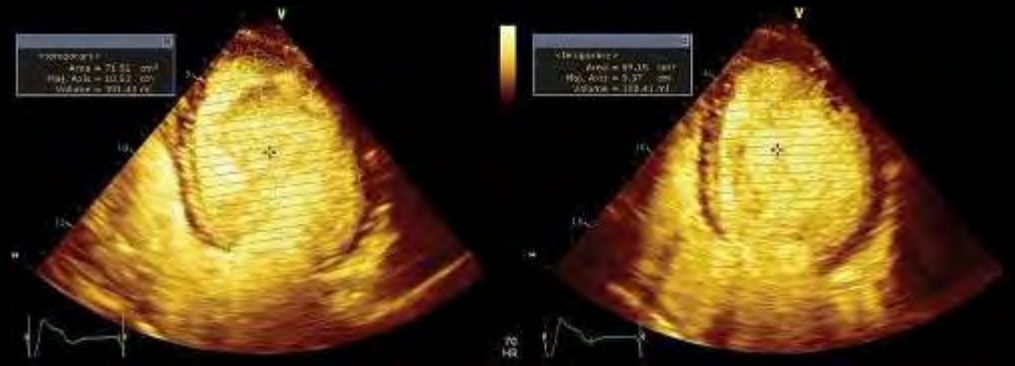
- ✓ *Early (EGE) and Late gadolinium enhancement (LGE) images were obtained at 2 and 10 minutes following injection of 0.2 mmol/Kg Gadolinium. Interpretation: UNMC, USA*



Echocardiography by IE33 – Philips Medical Systems

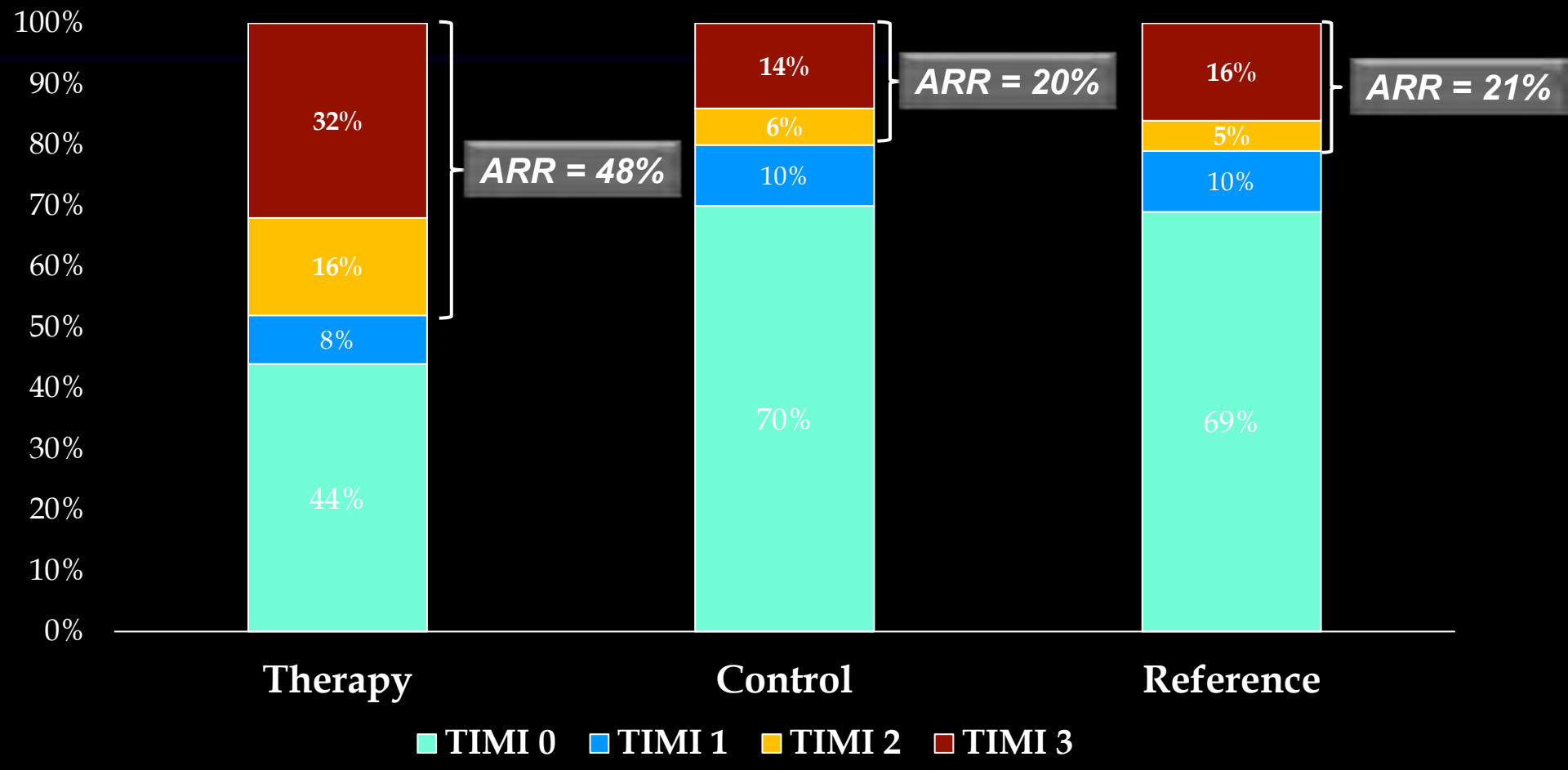
- ✓ *A score of 1: normal perfusion; 2: >4 second delay; 3: absent replenishment at 10 seconds post high MI impulse (MVO).*
- ✓ *EDV, ESV and Ejection Fraction were computed by contrast images using Simpson's Rule.*
- ✓ *Interpretation: two experienced cardiologists blinded to treatment assignment (InCor, Brazil and UNMC-Nebraska)*





Botker HE et al. J Cardiovas Magn Reson., 14;68, 2012.
Lang RM et al. J Am Soc Echocardiogr 28:1–39, 2015.
Porter TR et al. 31, 241-274, 2018.

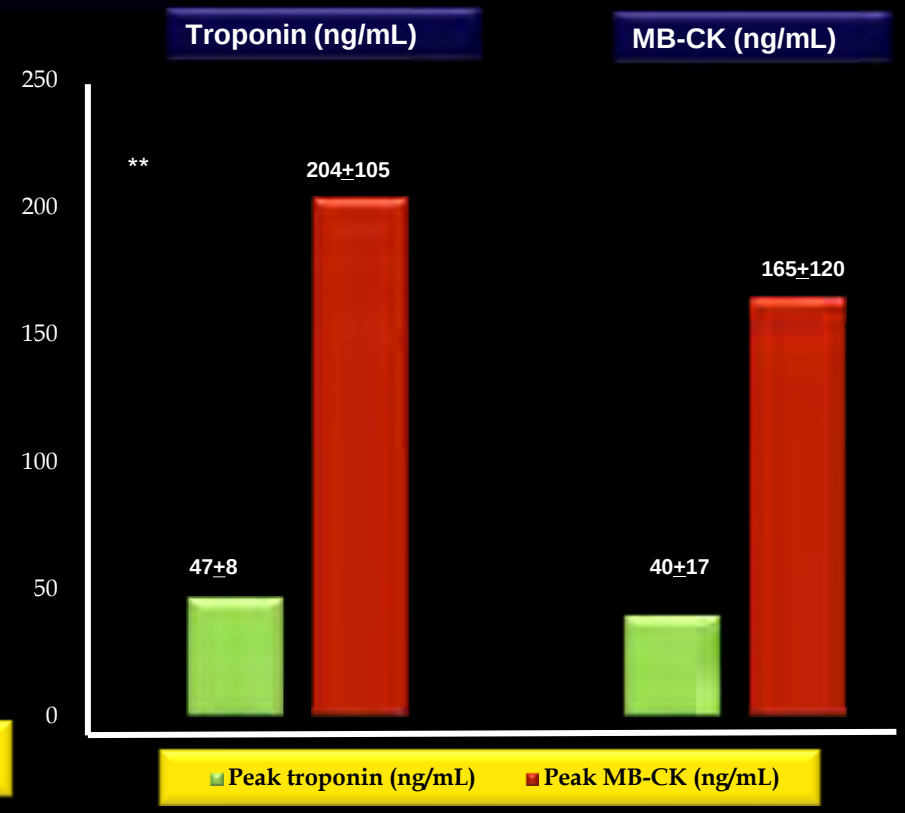
Angiographic Recanalization Rate Pre PCI



p < 0.001 between groups

Mathias W et.al. J Am Coll Cardiol 2019;73:2832-42

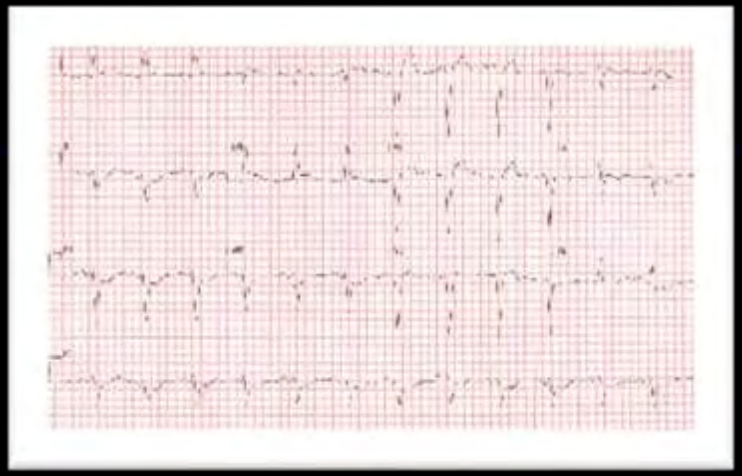
ST Segment Resolution and Peak Troponin/MBCK Values



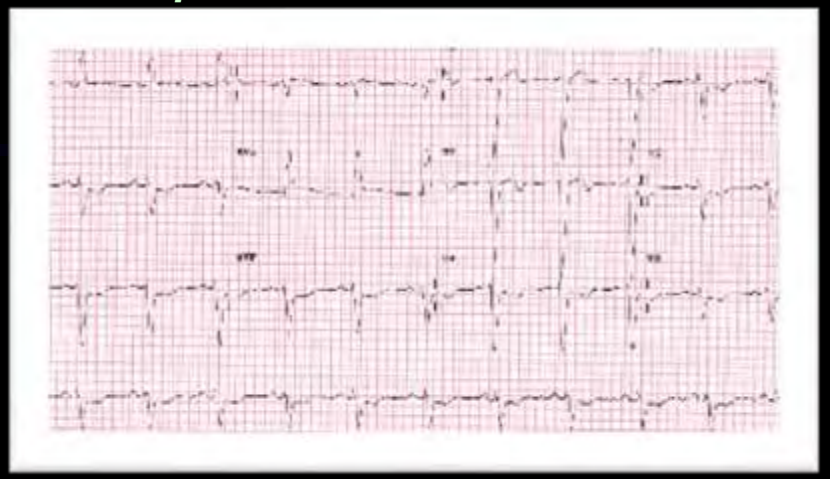
Mathias W et.al. J Am Coll Cardiol 2019;73:2832-42

Clinical Case

EKG at arrival



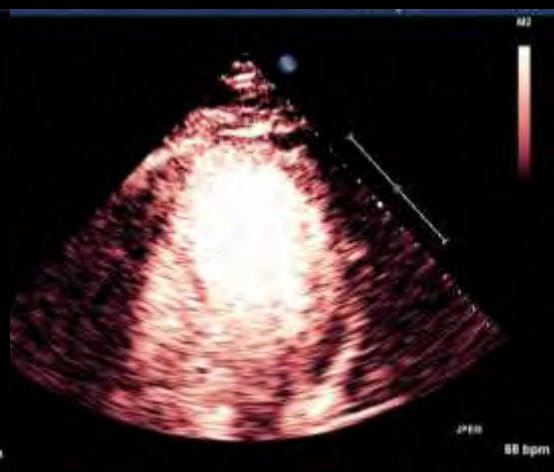
EKG post PCI



Beginning of Sonothrombolysis

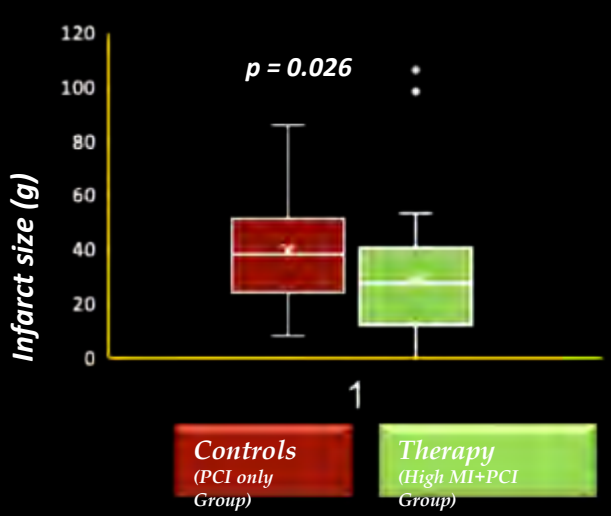
At 12 minutes of Sonothrombolysis

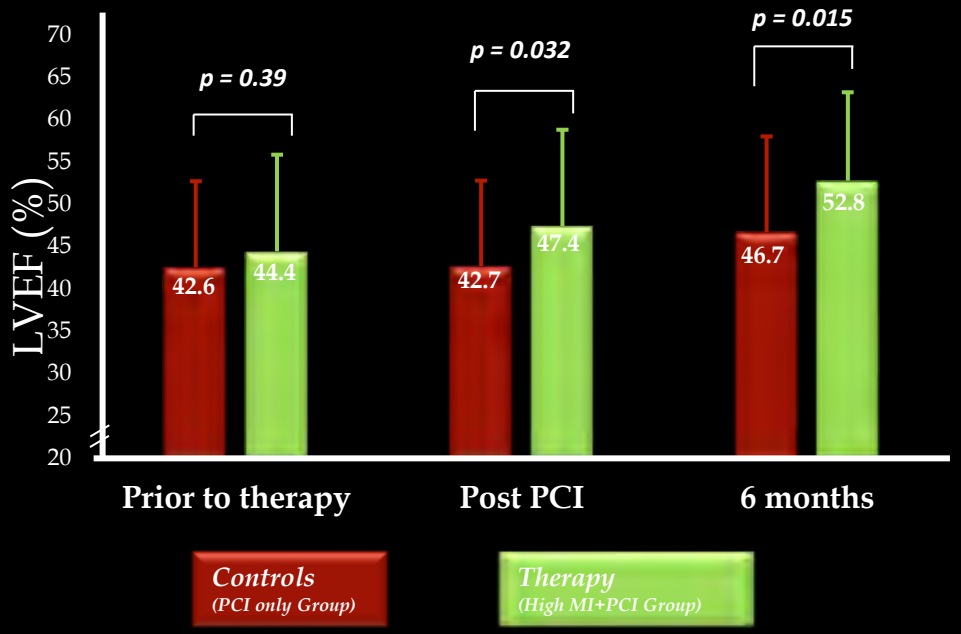
Echo post PCI



LVEF 29%

Infarct Size by MRI and LVEF by Echo



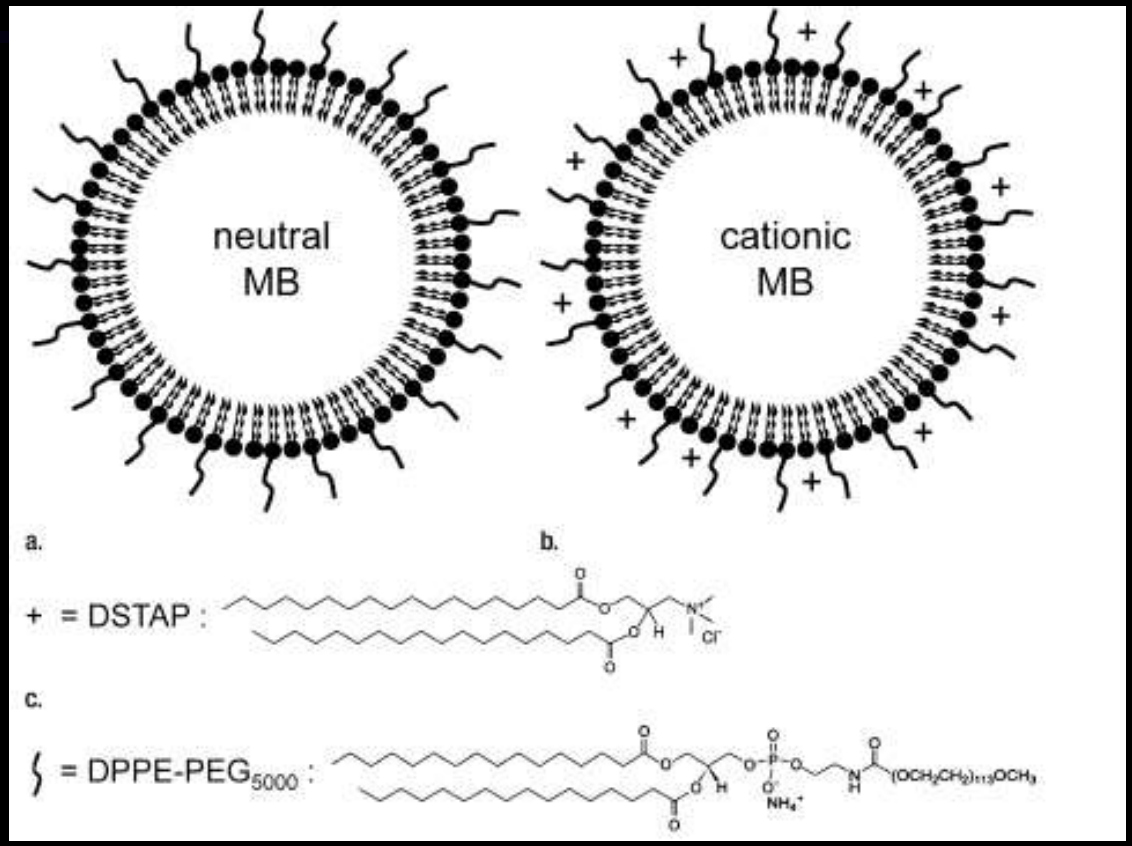


Mathias W et.al. J Am Coll Cardiol 2019;73:2832-42

Microvascular Theranostics

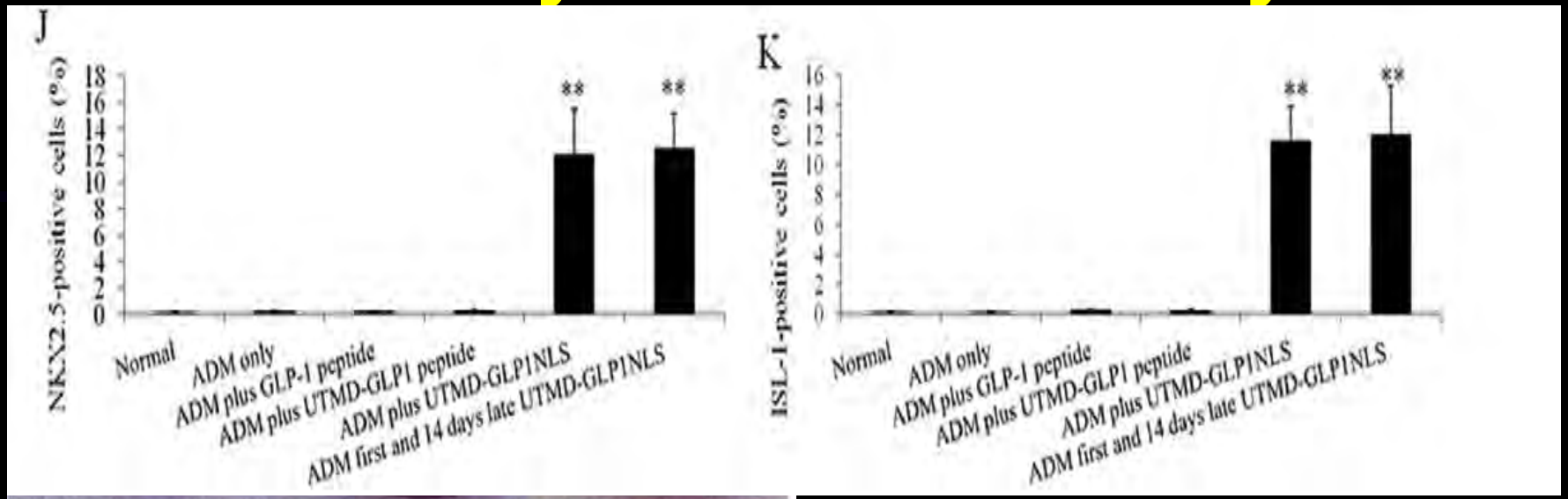
- Targeted Diagnostic High MI Applications
  - Improve Microvascular Flow
    - In Skeletal Muscle of PVD patients
    - In Microvascular Obstruction post MI
    - Targeted Drug/Gene Delivery

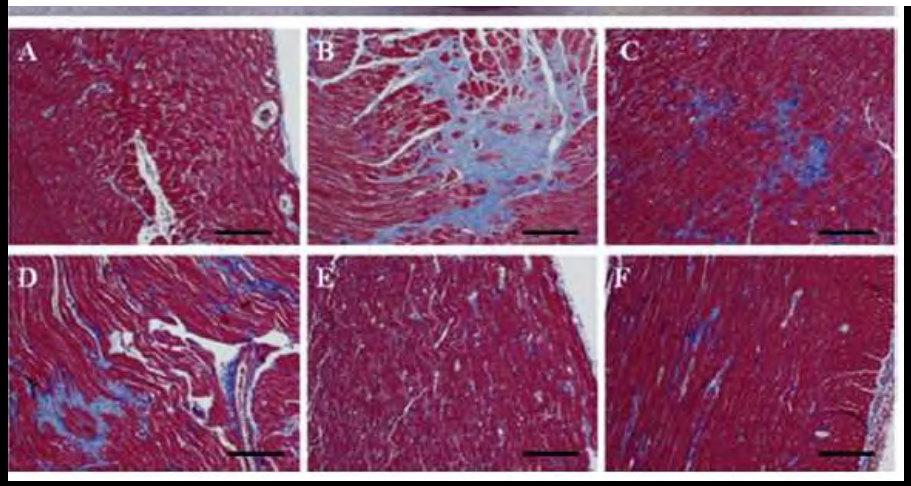
Targeted Delivery-CV Applications



Wang D et.al. Radiology 2012;264:721-32

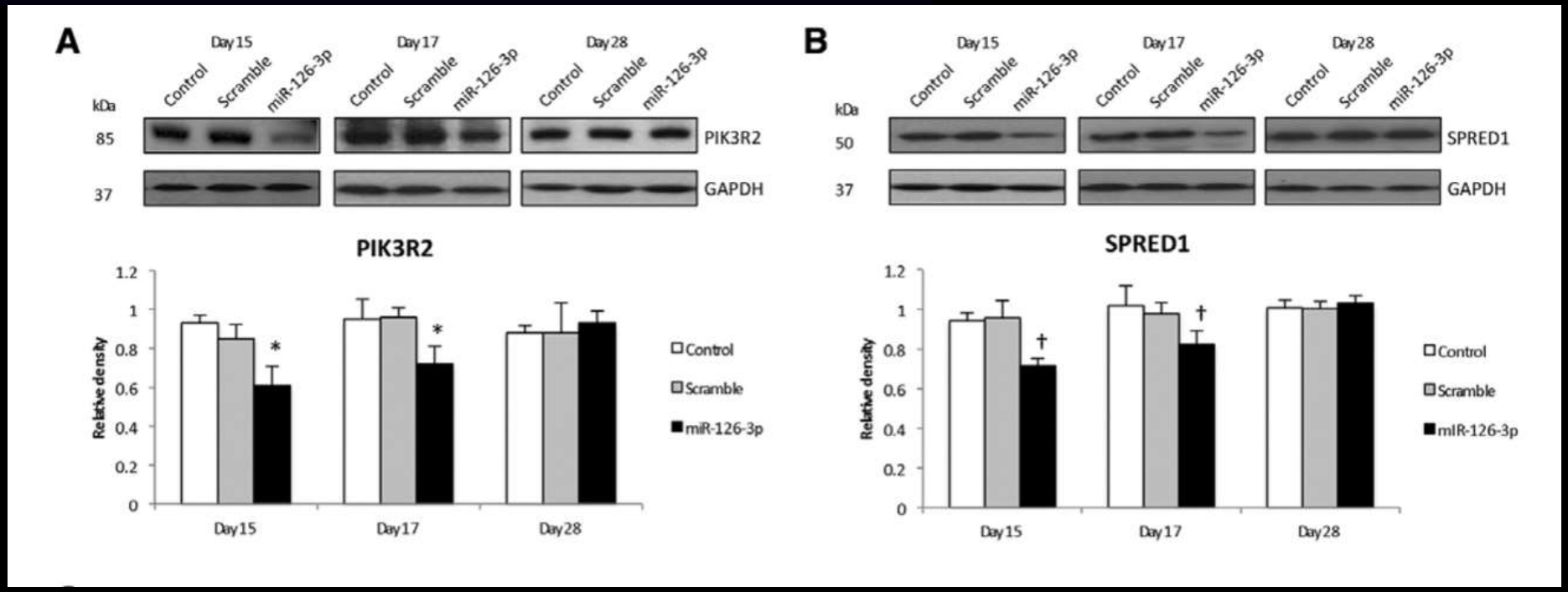
Adriamycin Cardiotoxicity





Chen S et.al. Biochemical and Biophysical Res Comm 2015: 823e829

Targeted Therapy in PAD
UTMD of miR 126-33p CMB



60,000 miR 126-33p molecules/MB

Cao WJ et.al. Arterioscler Thomb Vasc Biol 2015;35:2401-11