

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

Wilson Mathias, Jr¹, Jeane M Tsutsui¹, Bruno G Tavares¹, Agostina Fava², Miguel O D Aguiar¹, Bruno C Borges¹, Mucio T Oliveira Jr¹, Alexandre Soeiro¹, Jose C Nicolau¹, Henrique B Ribeiro¹, Hsu Pochiang¹, João C N Sbrano¹, Abdul Morad², Andrew Goldsweig², Carlos E Rochitte¹, Bernardo B C Lopes¹, José A F Ramirez¹, Roberto Kalil Filho¹, Thomas R Porter².



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



State of São Paulo, Government Agency
"BRAZILIAN NIH"



CIÊNCIA E HUMANISMO

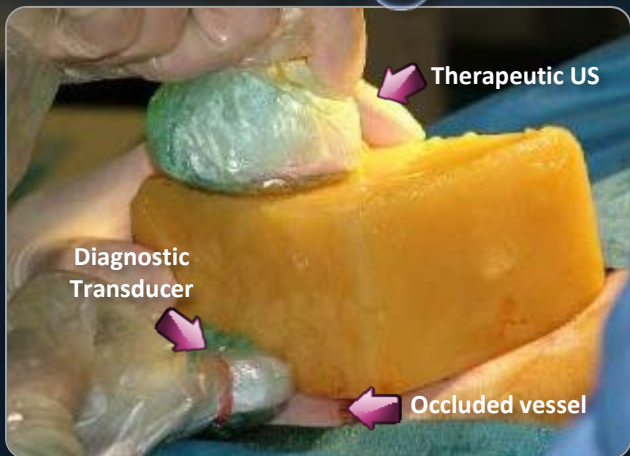
Heart Institute (InCor)

University of São Paulo Medical School
São Paulo, Brazil



Theodore F. and Claire M.
Hubbard Family Foundation

BACKGROUND

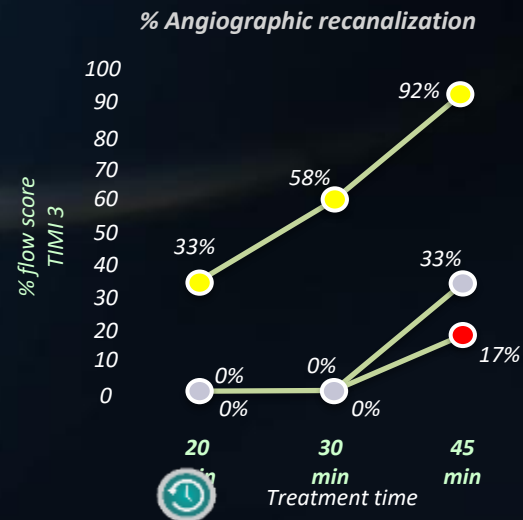


High Energy – IM > 1.0

12 Dogs – Thrombotic Occlusions

Tissue 6 cm

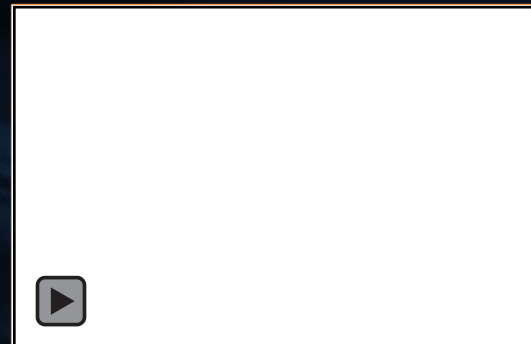
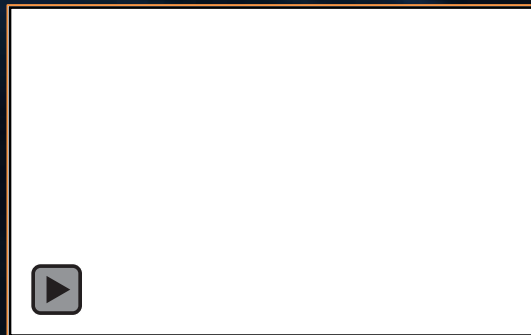
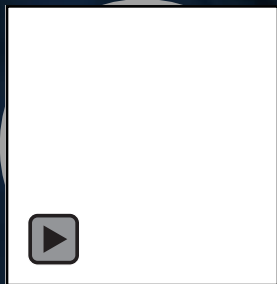
Therapeutic US 1 MHz



Occluded Graft

Low MI Imaging
Small channels despite
Graft Occlusion

Increase in Channels size
After Intermittent
High MI US



Coronary Reperfusion Therapies in 2019


Drawbacks



Fibrinolysis: Major Haemorrhagic Complications can Occurs in ~ 17%



Recanalization occurs in ~ 60% cases when patients present in <4h of pain



Fibrinolysis and PCI are Available in Brazil to only ~40% of patients



No reflow phenomena occurs in ~35 % of Cases


Study Design



Prospective, single-center, two arm randomized study



Patients with 1st ST elevation AMI



May 2014 – July 2018




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FAPESP # 2010/52114-1

OBJECTIVES



1 – *To determine the safety and feasibility sonothrombolysis in humans during acute STEMI in 100 patients*



2 – *To determine the potential efficacy of sonothrombolysis in achieving early infarct vessel patency and restoring left ventricular systolic function and reducing MI size*

Study Workflow

Emergency Room

Interventional Lab

Imaging Lab

Follow-up

Therapy Group
(n = 50)

Primary
PCI

Sonothrombolysis: intravenous microbubbles +
intermittent High MI impulses pre/post PCI
Median Time: 50 minutes

Clinical data
Pre-angio Echo
Biomarkers
EKG

Door to
balloon
time

ARR pre-PCI
Post-treatment Echo
Biomarkers
EKG

48-72h MRI and
Echo

1-month Echo
Follow-up data

6-month Echo
Follow-up data

Control Group
(n = 50)

Primary
PCI

Intravenous microbubbles +
3 sets of Low MI images

Reference Group
(n = 203)

Primary
PCI

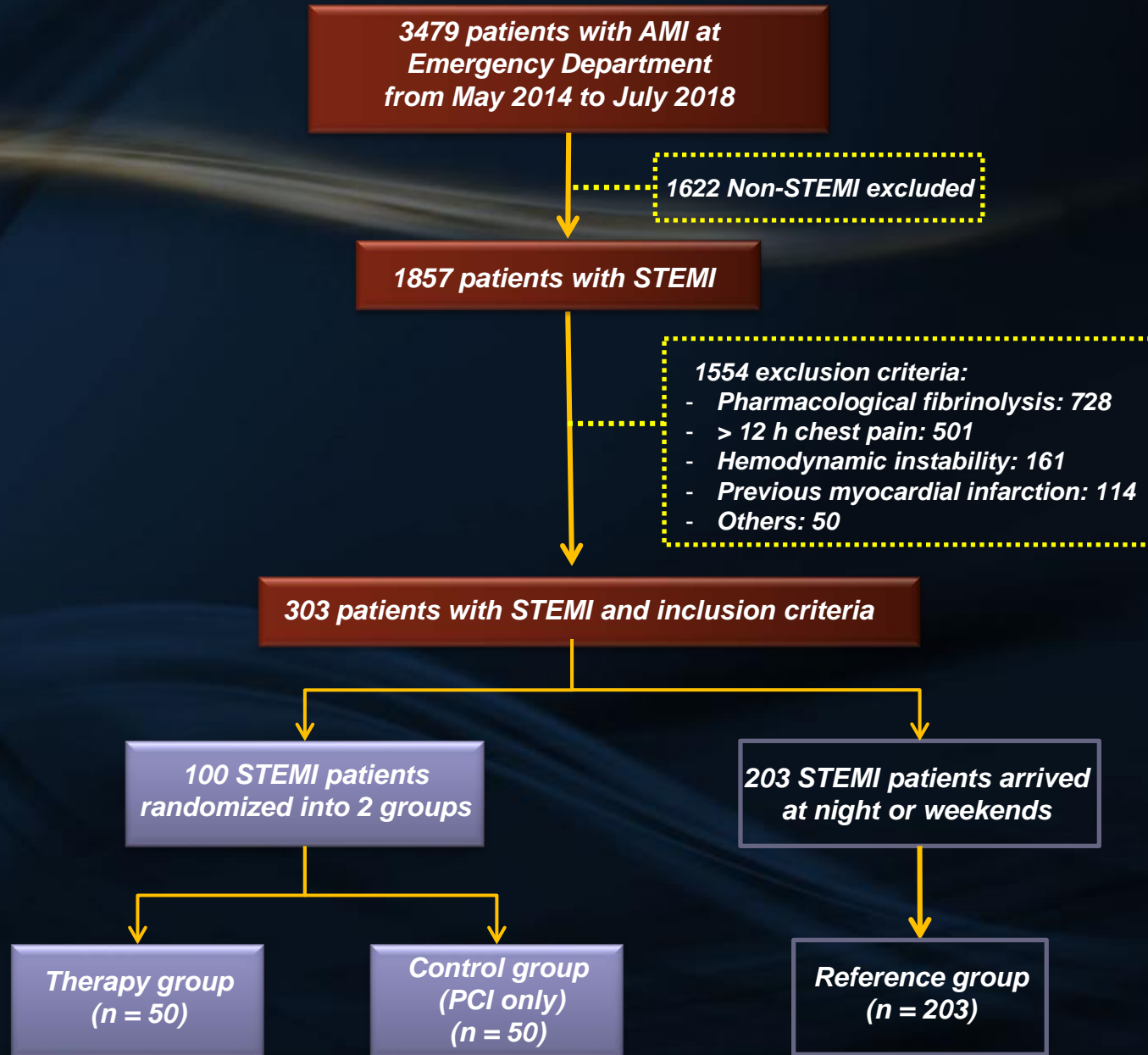
• Clinical data

• ARR pre-PCI

Randomization

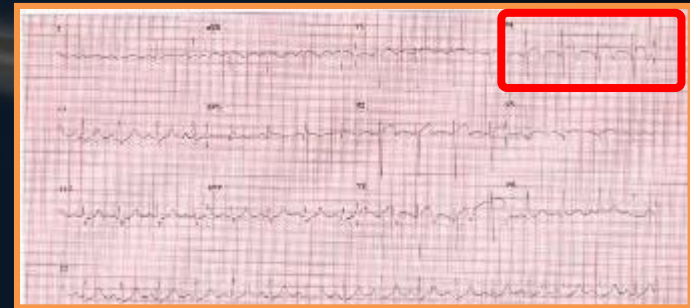
Arrival at night
Weekends / Holidays

Patient Selection



Elektrocardiogram, Biomarkers and Angiography

- ✓ *ST segment resolution as a % or $\geq 50\%$ ST resolution from baseline to Post sonolysis pre PCI and at the end of the second sonolysis (*).*



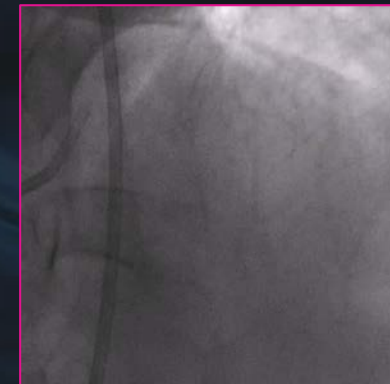
- ✓ *Cardiac specific troponin and creatinine kinase MB fraction (CPK MB) every 3 hours for 18 hours.*

Closed artery – TIMI 0 and 1



Interpretation: UNMC, USA

Opened artery – TIMI 2 and 3



Echocardiography and MRI Imaging

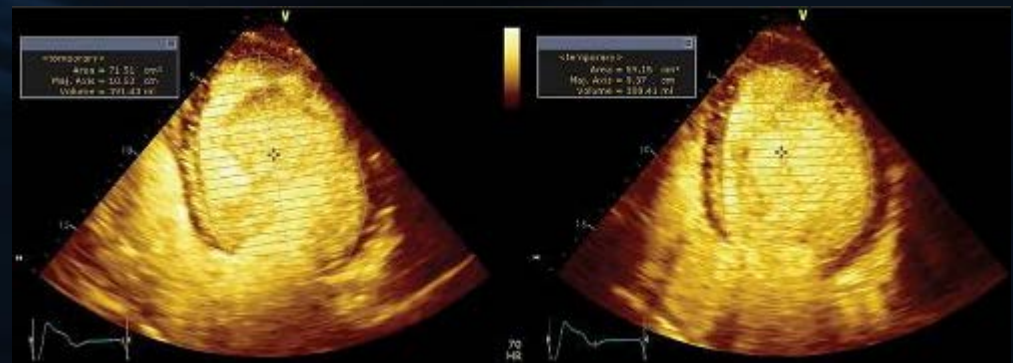
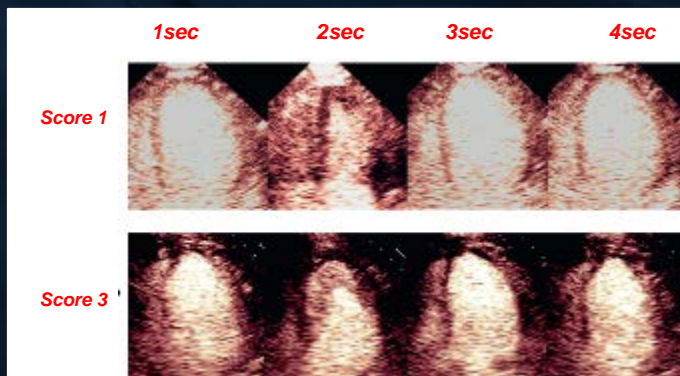
MRI by Achieva de 1,5T, Philips Medical Systems

- ✓ 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: experienced cardiologist blinded to treatment assignment at the recruitment center (InCor, Brazil)



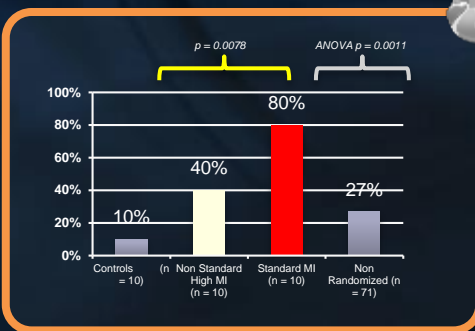
Botker HE et al. J Cardiovas Magn Reson., 14;68, 2012.

Lang RM et al. J Am Soc Echocardiogr 28:1–39, 2015.

Porter TR et al. 31, 241-274, 2018.

Statistics

- ✓ Based on pilot data (*), we anticipated randomizing 100 patients to achieve statistical significance ($p < 0.05$) using unpaired one-tailed t testing for continuous variables.
- ✓ Data were analyzed for possible confounders, including demographics, patient medications, and disease characteristics. We expected the High MI/PCI group to have $\geq 50\%$ ST segment resolution in 80% of cases versus 50% of cases in the PCI only group after all interventions were completed.
- ✓ We also projected an expected early angiographic patency rate of at least 50% in the High MI/PCI group versus 20% in the PCI only group.



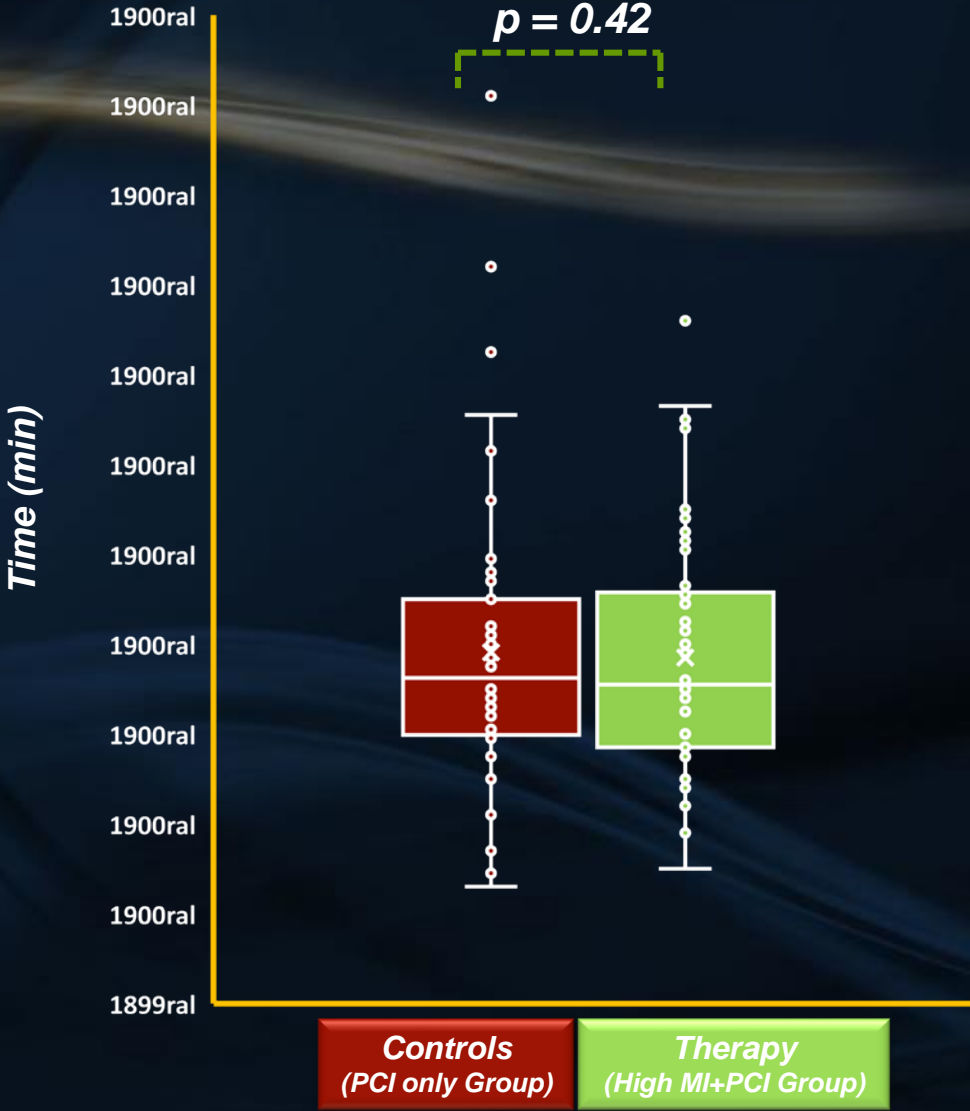
- ✓ Primary outcomes: rate of ST segment resolution and angiographic patency prior to PCI as continuous and dichotomous variable.
- ✓ Secondary outcomes: Infarct size by CMRI and microvascular flow, LVEF and Myocardial Perfusion at baseline, post PCI, one week and six months. Differences were compared between groups at specific time points, and no adjustments were made for multiple comparisons over time.
- ✓ Proportional differences were compared using contingency tables with Chi Square X^2 testing 2x2 contingency tables or Fisher's Exact test if < 5 in any sample size.
- ✓ Analysis of Variance was used for comparisons of continuous variables in the high MI/PCI versus PCI only and Reference groups.

Demographic Variables

	Control Group	Therapy Group	Reference Group	
Variable	n = 50	n = 50	n = 203	p Value
Age (years)	59±11	59±10	59+11	0.96 ⁽¹⁾
Gender (male)	40 (80%)	32 (64%)	148 (73%)	0.20 ⁽²⁾
Weight (kg)	77±16	74±16	76+13	0.65 ⁽¹⁾
BSA (m ²)	1.86 + 0.22	1.82 + 0.22	1.82 + 0.19	0.41 ⁽¹⁾
Diabetes	11 (22%)	21 (42%)	67 (33%)	0.10 ⁽²⁾
Hypertension	28 (56%)	28 (56%)	118 (58%)	0.95 ⁽²⁾
Hyperlipidemia	15 (30%)	20 (40%)	55 (27%)	0.20 ⁽²⁾
Smoking	20 (40%)	24 (48%)	70 (34%)	0.20 ⁽²⁾
Medication in use				
Statin	14 (28%)	19 (38%)	21 (10%)	<0.001 ⁽²⁾
Beta blocker	5 (10%)	14 (28%)	27 (13%)	0.019 ⁽²⁾
Aspirin	50 (100%)	48 (96%)	202 (99%)	0.14 ⁽³⁾
Nitrate	25 (50%)	27 (54%)	95 (47%)	0.64 ⁽²⁾
Calcium channel Blocker	4 (8%)	5 (10%)	14 (7%)	0.72 ⁽³⁾
STEMI arterial territory				
LAD	26 (52%)	26 (52%)	90 (44%)	0.83 ⁽²⁾
RCA	14 (28%)	17 (34%)	84 (41%)	
LCX	10 (20%)	7 (14%)	29 (14%)	

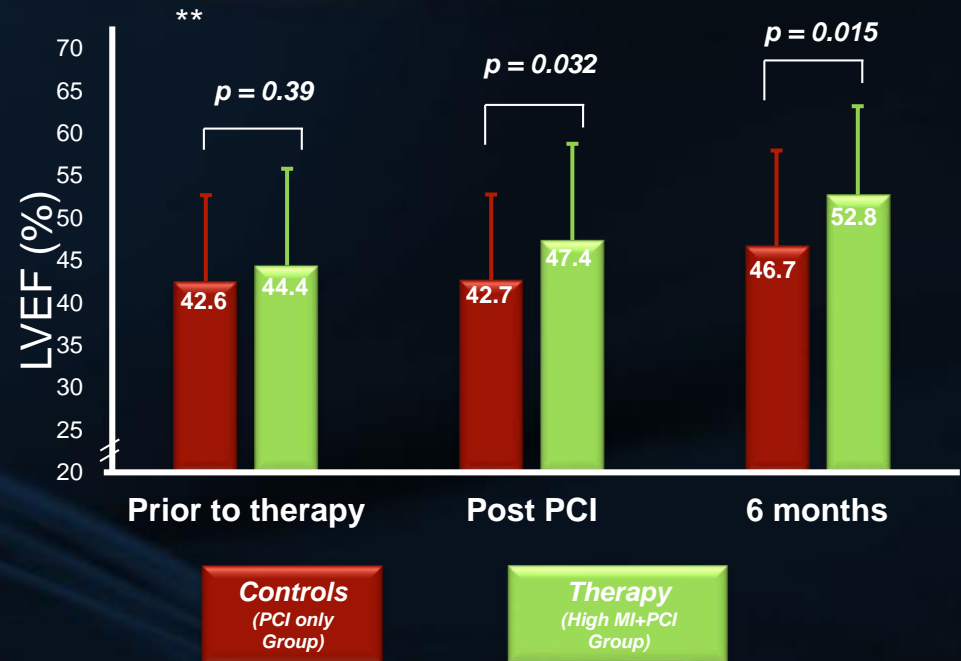
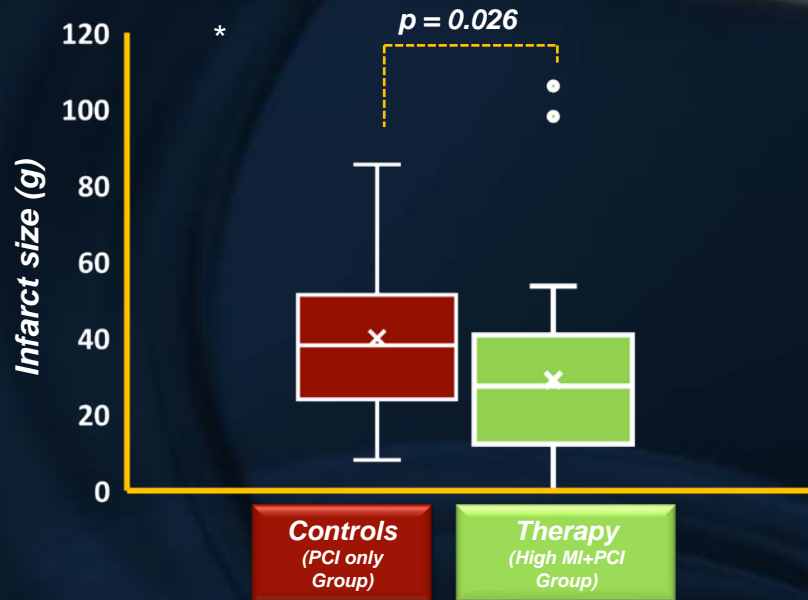
Variables expressed as mean ± standard deviation or number (%). (1) Analysis of variance; (2) Chi- square test; (3) Fisher Exact test.

Door to Balloon Time



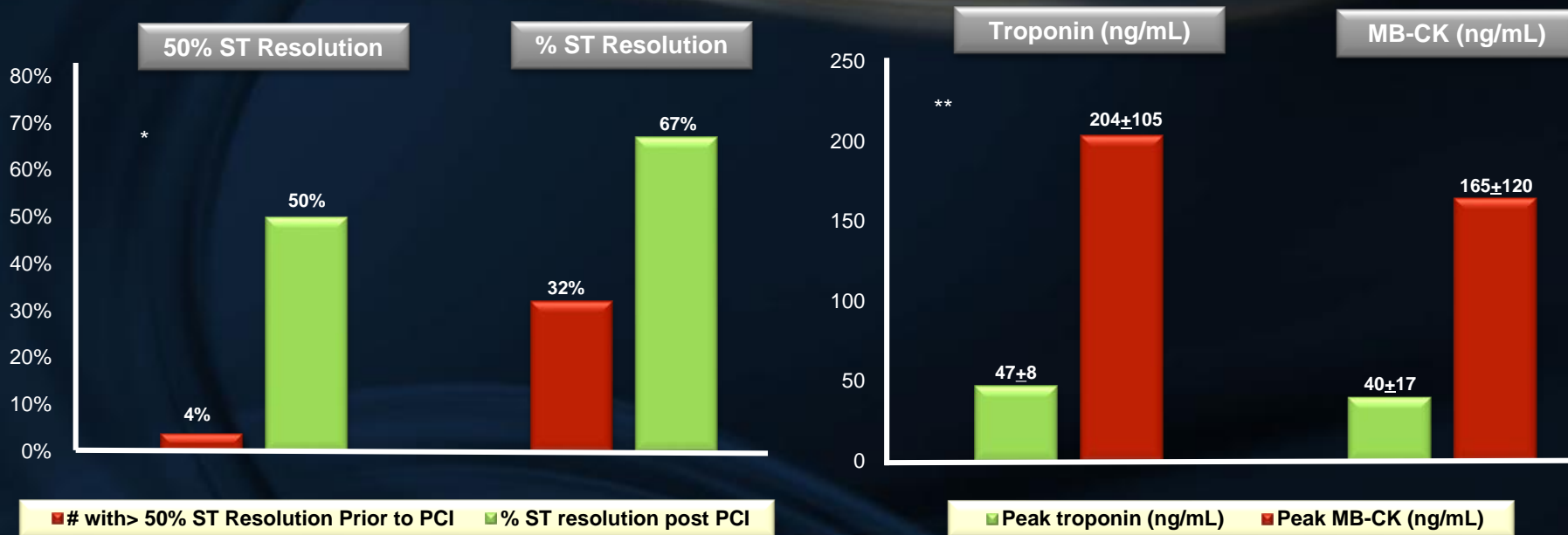
Chi Square X2 or Fisher's Exact test (CREUSA CHECAR!!)

Infarct Size by MRI and LVEF by Echo



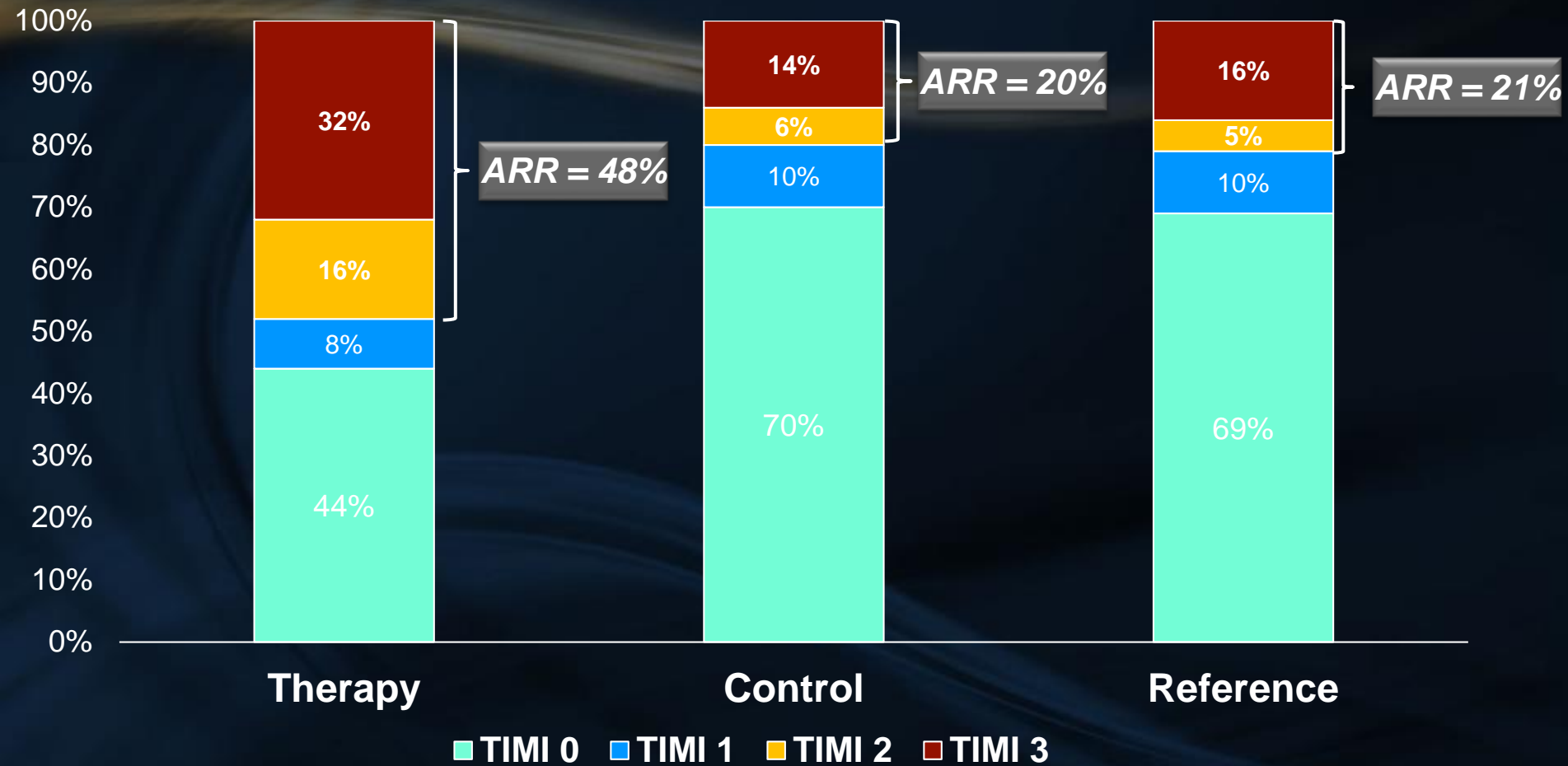
(*) Mann Whitney test; (**) Student T test.

ST Segment Resolution and Peak Troponin/MBCK Values



(*) Mann-Whitney test; (**) Student T test.

Angiographic Recanalization Rate Pre PCI



Chi Square X2 or Fisher's Exact test (CREUSA CHECAR!!)

$p < 0.001$ between groups

Clinical Case # 14

Randomized to Control Group



ROM, 48 y/o



Smoker (20 cig/day)



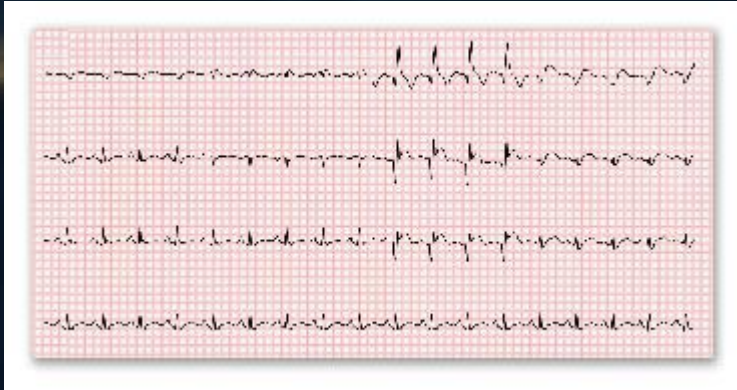
Hypertensive & Dyslipidemia



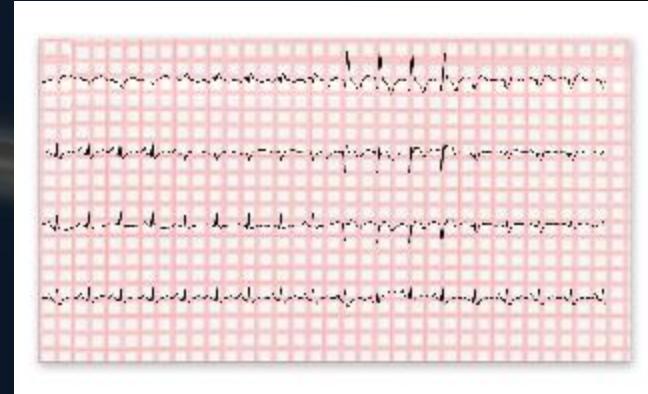
Continuous chest pain (7/10 Scale), for ~2 Hours

Clinical Case # 14

EKG at arrival



EKG post PCI



Echo at arrival



Echo post PCI

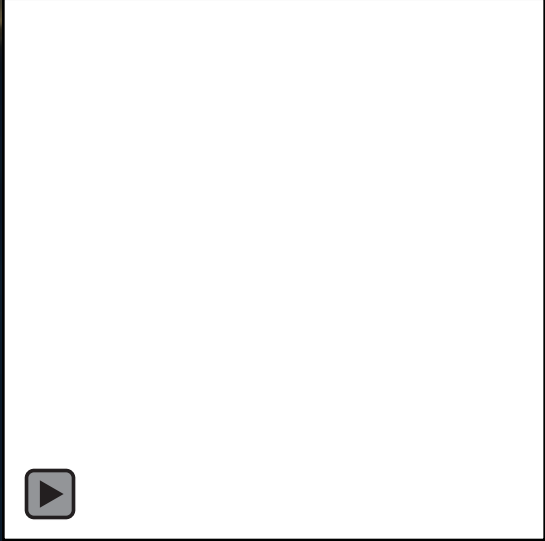


LVEF 26%

Clinical Case # 14

Coronary Angiography

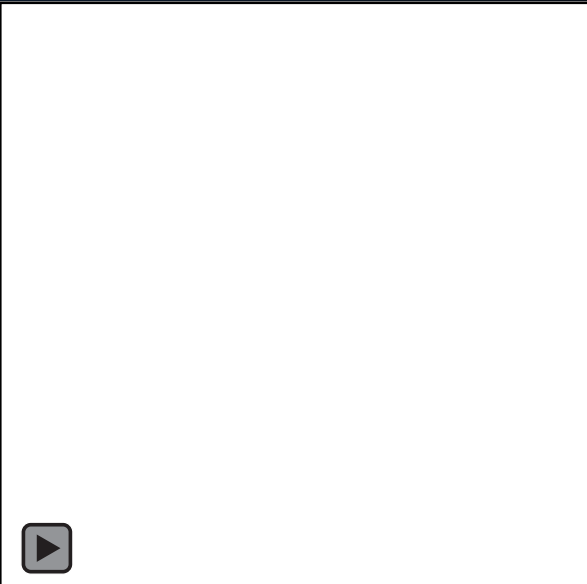
Before PCI



Post PCI



72h MRI



Clinical Case # 76

Randomized to Therapy Group



CAF, 52y/o Male



Hypertensive



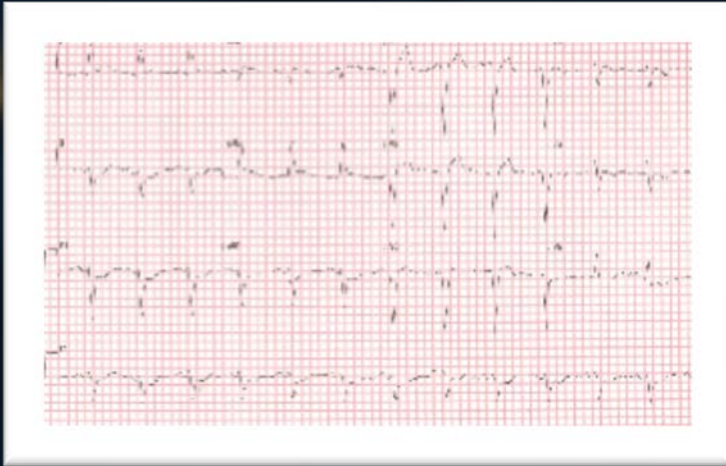
Dyslipidemia



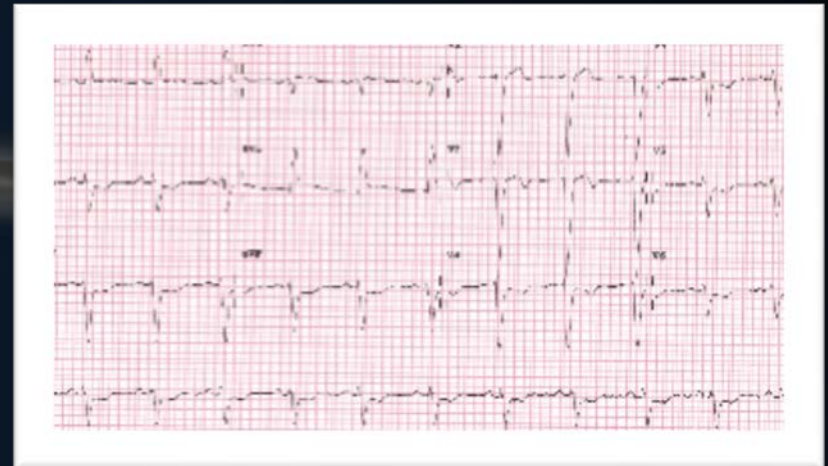
Continuous chest pain (9/10 Scale) for ~1:45h

Clinical Case # 76

EKG at arrival



EKG post PCI



Beginning of Sonothrombolysis



At 12 minutes of Sonothrombolysis



Echo post PCI

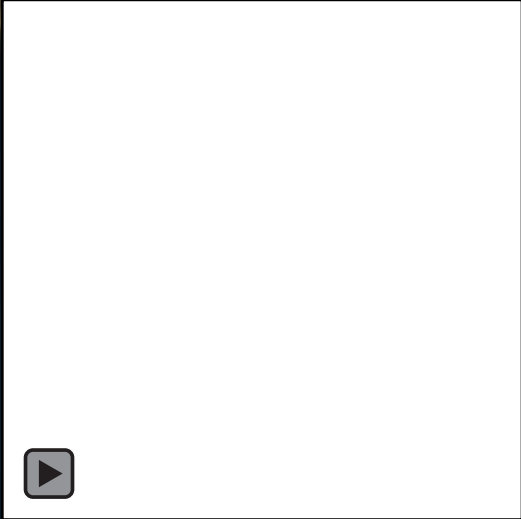


LVEF 29%

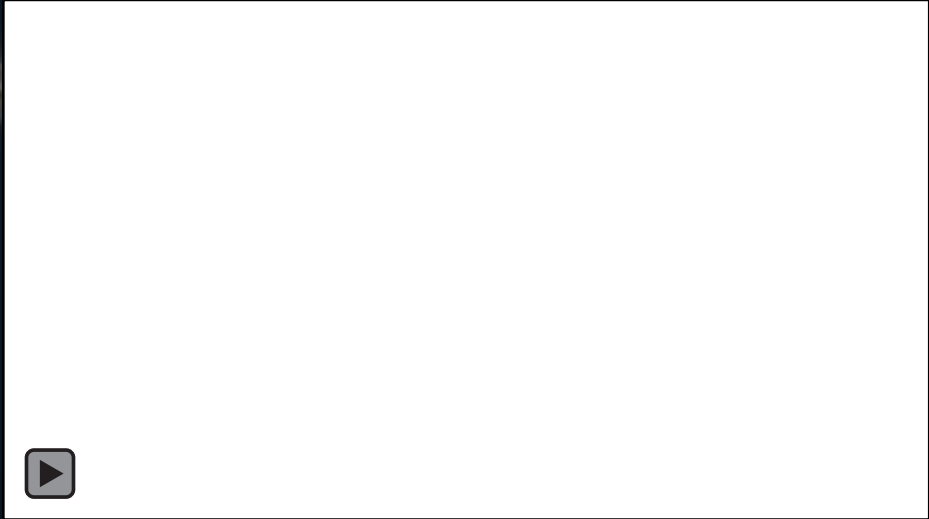
Clinical Case # 76

Coronary Angiography

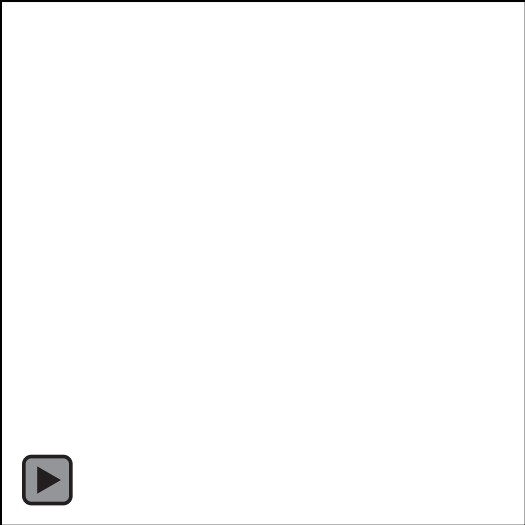
Before PCI



72h MRI



Post PCI

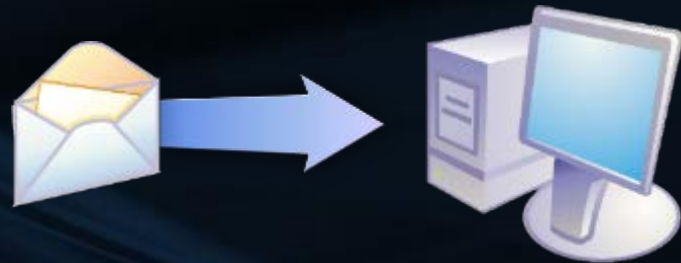




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1 – Sonothrombolysis in humans is safe and feasible in patients with STEMI

2 –Sonothrombolysis is efficacious in achieving early infarct vessel patency and restoring left ventricular systolic function and reducing MI size.



Thank you

wmathias@incor.usp.br