Reperfusion Injury: How Can We Reduce It?

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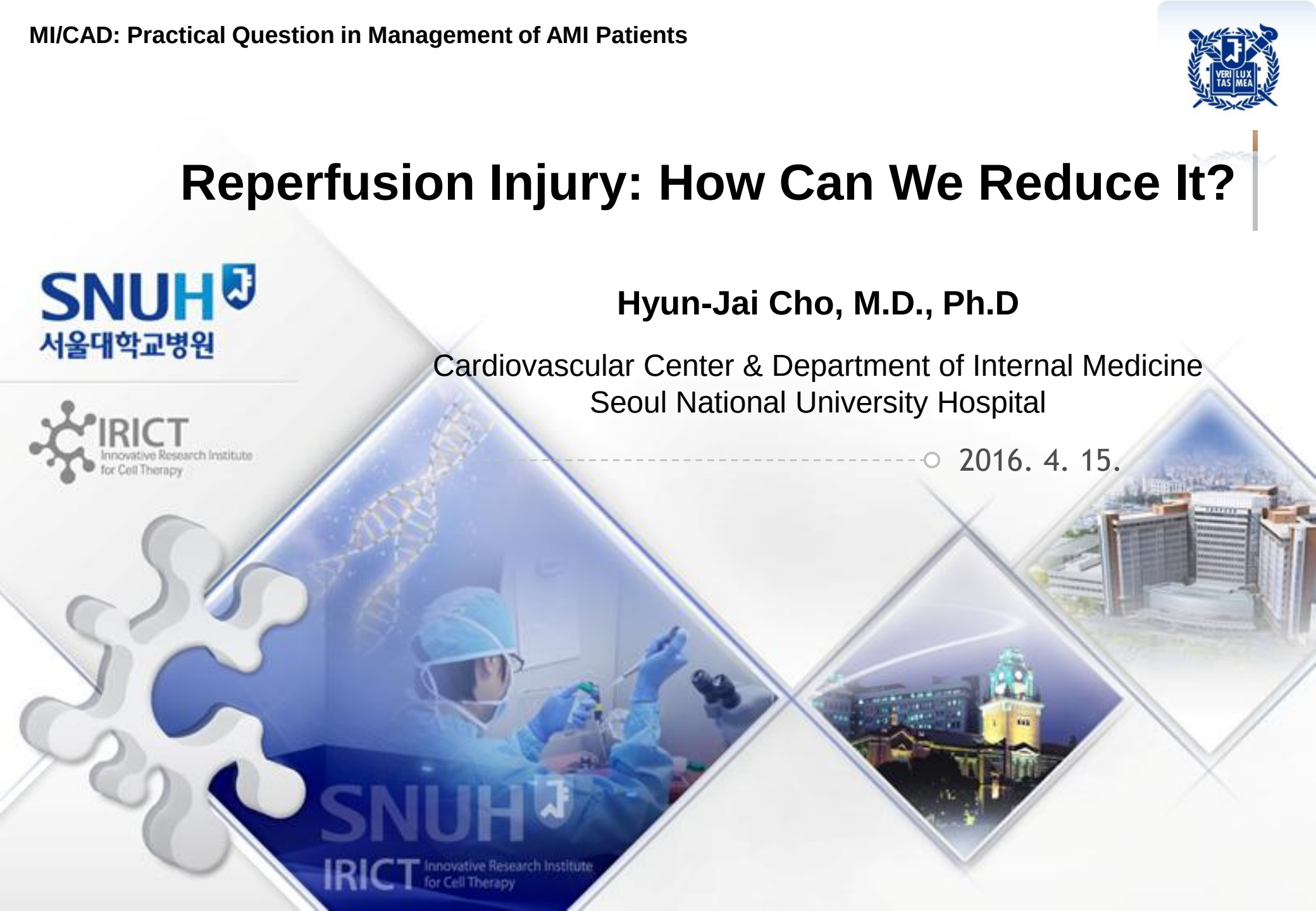
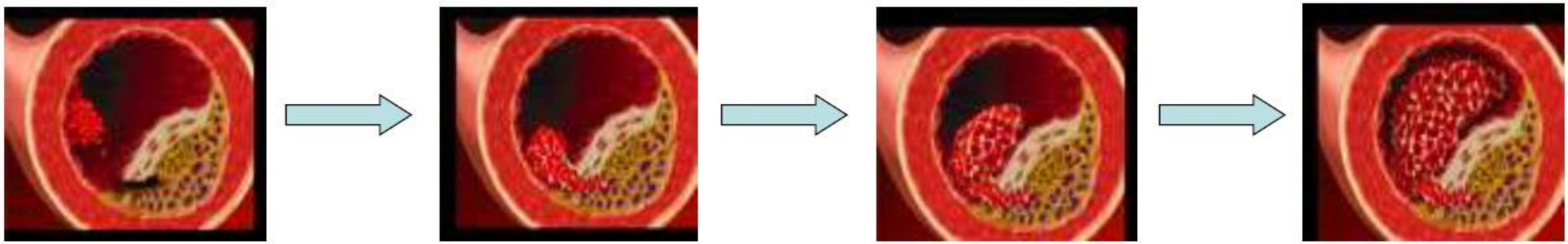
2016. 4. 15.

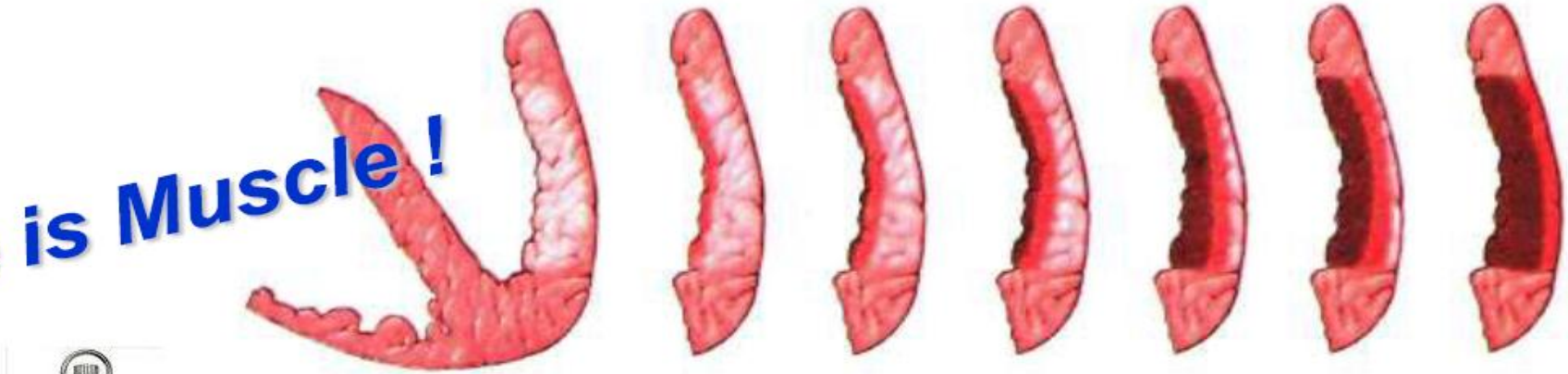


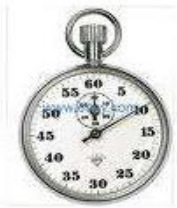
Acute Myocardial Infarction

Rupture of atheromatous plaque in the coronary artery
Platelet aggregation and thrombus formation
Occlusion of the coronary artery



Time is Muscle !





Onset	<20-40 min	30 min	1 hour	2 hours	4 hours	6 hours
	0%	10%	30%	50%	70%	90%

Time is Myocardium !

- Treatment flow for STEMI

Early reperfusion therapy

: the first priority in the treatment of STEMI

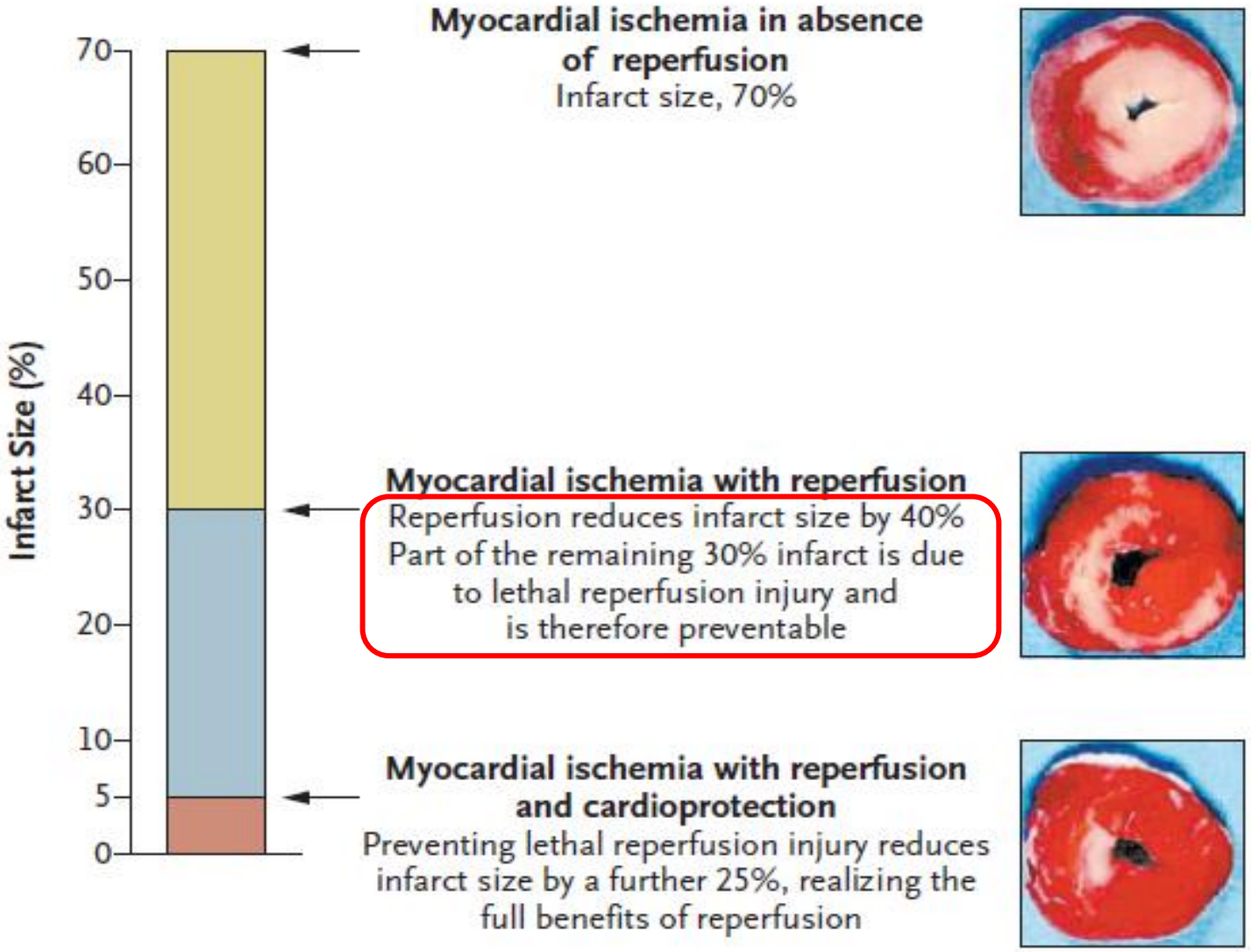
- thrombolytic therapy
- Percutaneous coronary intervention (PCI)

Reperfusion

Reperfusion immediately causes myocyte necrosis and sarcolemmal disruption, with the leakage of cell contents into the extracellular space.

Apoptosis is a coordinated involution of myocytes that circumvents the inflammation associated with **necrotic cell death**. Because apoptosis is an energy-dependent process, cells can be forced to switch to a necrotic pathway if energy levels are depleted below critical levels.

In more chronic settings, autophagy can contribute to the mechanisms of myocyte death.

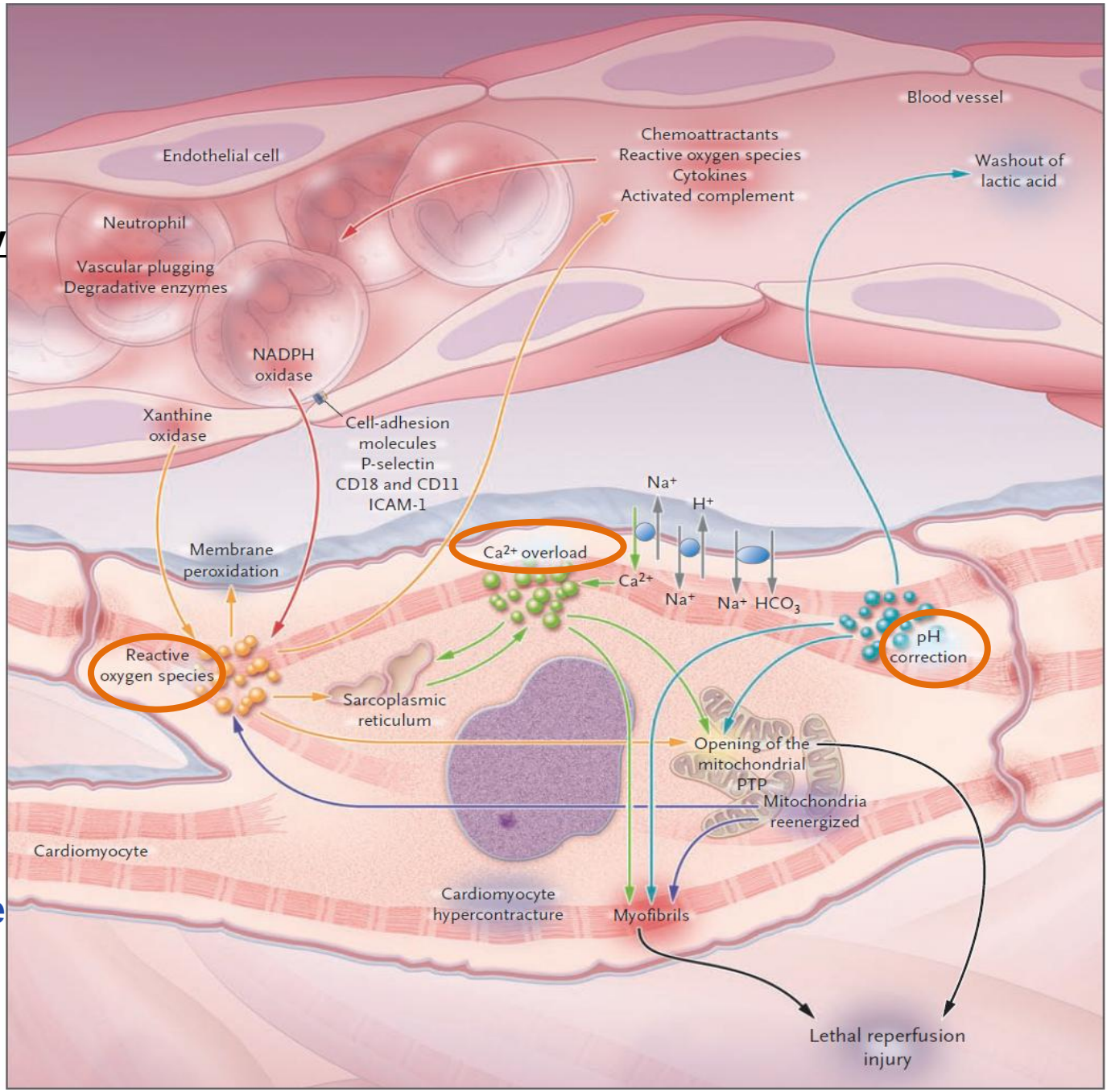

Infarct Size (%)
70
60
50
40
30
20
10
5
0
Myocardial ischemia in absence of reperfusion
Infarct size, 70%
Myocardial ischemia with reperfusion
Reperfusion reduces infarct size by 40%
Part of the remaining 30% infarct is due to lethal reperfusion injury and is therefore preventable
Myocardial ischemia with reperfusion and cardioprotection
Preventing lethal reperfusion injury reduces infarct size by a further 25%, realizing the full benefits of reperfusion

Ischemia-reperfusion injury

1. Oxygen paradox
2. Calcium paradox
3. pH paradox

4. Inflammation due to necrosis

Mitochondrial Permeability Transition Pore (mPTP) opening



[ISCHEMIA]

Oxygen and glucose depletion

↓

ATP depletion, anaerobic gylcolysis↑

↓

pH drop. $[Na^+]$↑, $[Ca^{2+}]$ ↑

↓

Mitochondria $[Ca^{2+}]$ overload

[REPERFUSION]

Reintroduction of oxygen
Rapid correction of acidosis

↓

Burst of reactive oxygen species
Ca^{2+} influx

↓

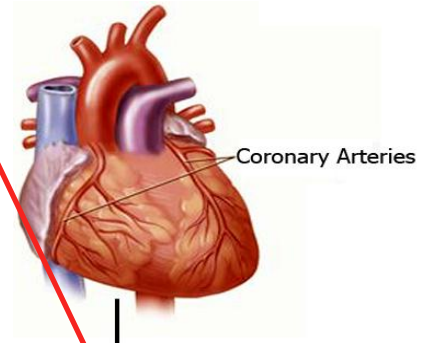
mPTP opening

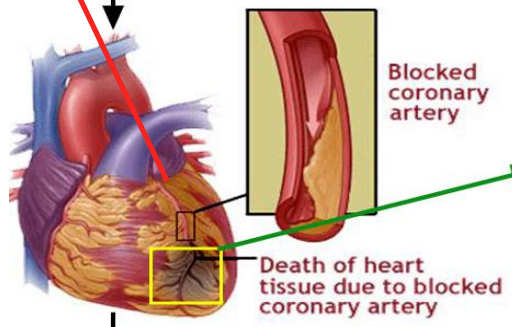
↓

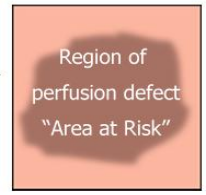
Mitochondria matrix swelling,
Outer mitochondrial membrane rupture
*Hallmark of necrosis

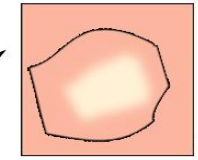
↓

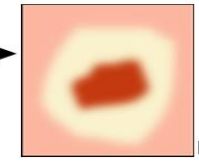
Necrotic cell death

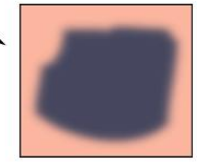


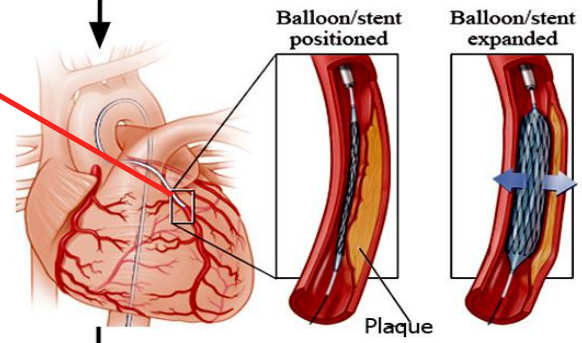


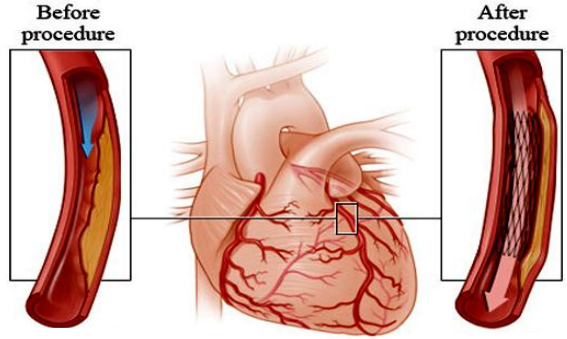


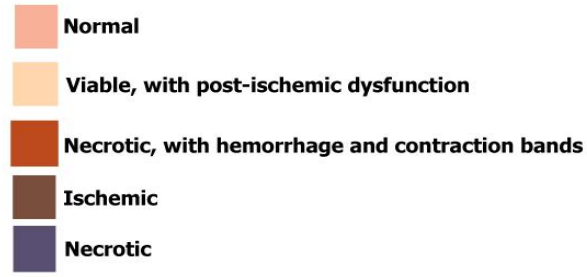












Ischemic conditioning to prevent I/R injury

The 30-year anniversary of the discovery of “ischemic preconditioning”

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.

ABSTRACT We have previously shown that a brief episode of ischemia slows the rate of ATP depletion during subsequent ischemic episodes. Additionally, intermittent reperfusion may be beneficial to the myocardium by washing out catabolites that have accumulated during ischemia.[1] Thus, we proposed that multiple brief ischemic episodes might actually protect the heart from a subsequent sustained ischemic insult. To test this hypothesis, two sets of experiments were performed. In the first set, one group of dogs (n = 7) was preconditioned with four 5 min circumflex occlusions, each separated by 5 min of reperfusion, followed by a sustained 40 min occlusion. The control group (n = 5) received a single 40 min occlusion. In the second study, an identical preconditioning protocol was followed, and animals (n = 9) then received a sustained 3 hr occlusion. Control animals (n = 7) received a single 3 hr occlusion. Animals were allowed 4 days of reperfusion thereafter. Histologic infarct size then was measured and was related to the major baseline predictors of infarct size, including the anatomic area at risk and collateral blood flow. In the 40 min study, preconditioning with ischemia paradoxically limited infarct size to 25% of that seen in the control group ($p < .001$). Collateral blood flows were not significantly different in the two groups. In the 3 hr study, there was no difference between infarct size in the preconditioned and control groups. The protective effect of preconditioning in the 40 min study may have been due to reduced ATP depletion and/or to reduced catabolite accumulation during the sustained occlusion. These results suggest that the multiple anginal episodes that often precede myocardial infarction in man may delay cell death after coronary occlusion, and thereby allow for greater salvage of myocardium through reperfusion therapy.

Circulation 74, No. 5, 1124–1136, 1986.

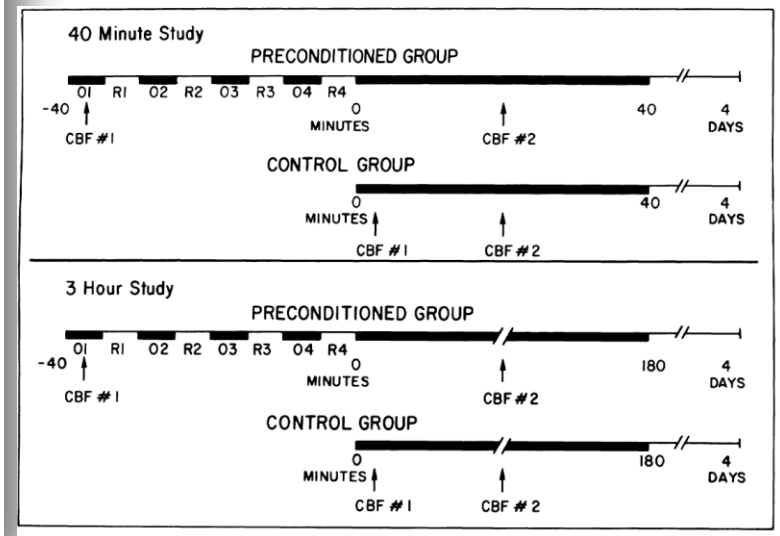
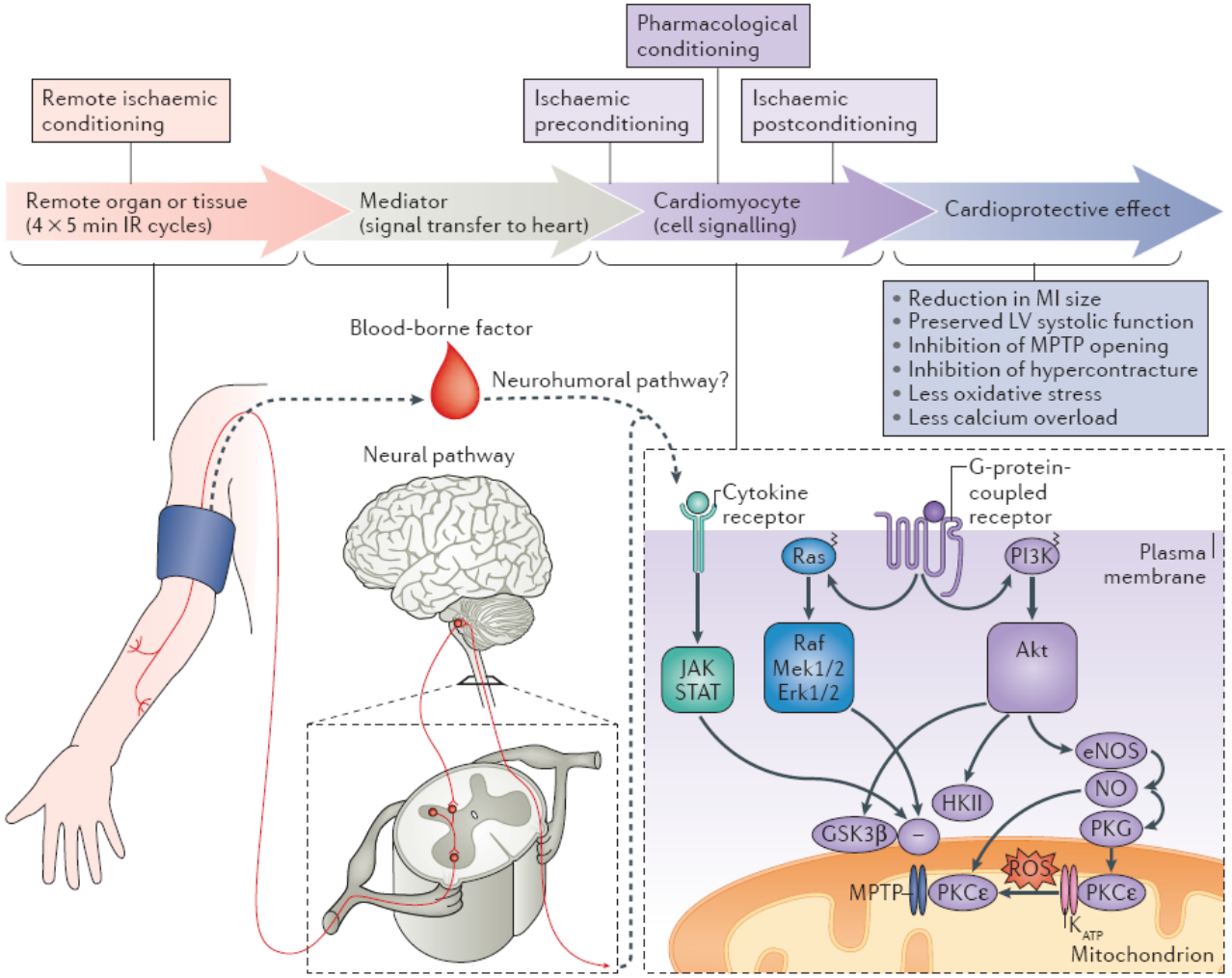


FIGURE 2. Experimental design. In the 40 min study, preconditioned animals underwent four 5 min circumflex coronary occlusions, each separated by 5 min of reperfusion, followed by a sustained 40 min occlusion. Control animals underwent a single 40 min occlusion. Collateral blood flow (CBF) in the preconditioned group was measured midway through the first 5 min occlusion and midway through the 40 min occlusion. CBF in the control group was measured 2.5 min into and midway through the 40 min occlusion. Both groups were allowed 4 days of reperfusion after the 40 min occlusion. In the 3 hr study, preconditioned animals underwent four 5 min circumflex coronary occlusions, each separated by 5 min of reperfusion, followed by a sustained 3 hr occlusion. Control animals underwent a single 3 hr occlusion. CBF in the preconditioned group was measured midway through the first 5 min occlusion and 105 min into the 3 hr occlusion. CBF in the control group was measured 2.5 min into and 105 min into the 3 hr occlusion. Both groups were allowed 4 days of reperfusion after the 3 hr occlusion. O = occlusion; R = reperfusion.

Signaling pathways of ischemic conditioning



1) Reperfusion Injury Salvage Kinase (RISK) pathway (PI3K–Akt and Mek1/2–Erk1/2)
2) Survivor Activator Factor Enhancement (SAFE) pathway (TNF and JAK–STAT),
3) cGMP–protein kinase G (PKG) pathway

→ **inhibitory effect on mitochondrial permeability transition pore (mPTP) opening**

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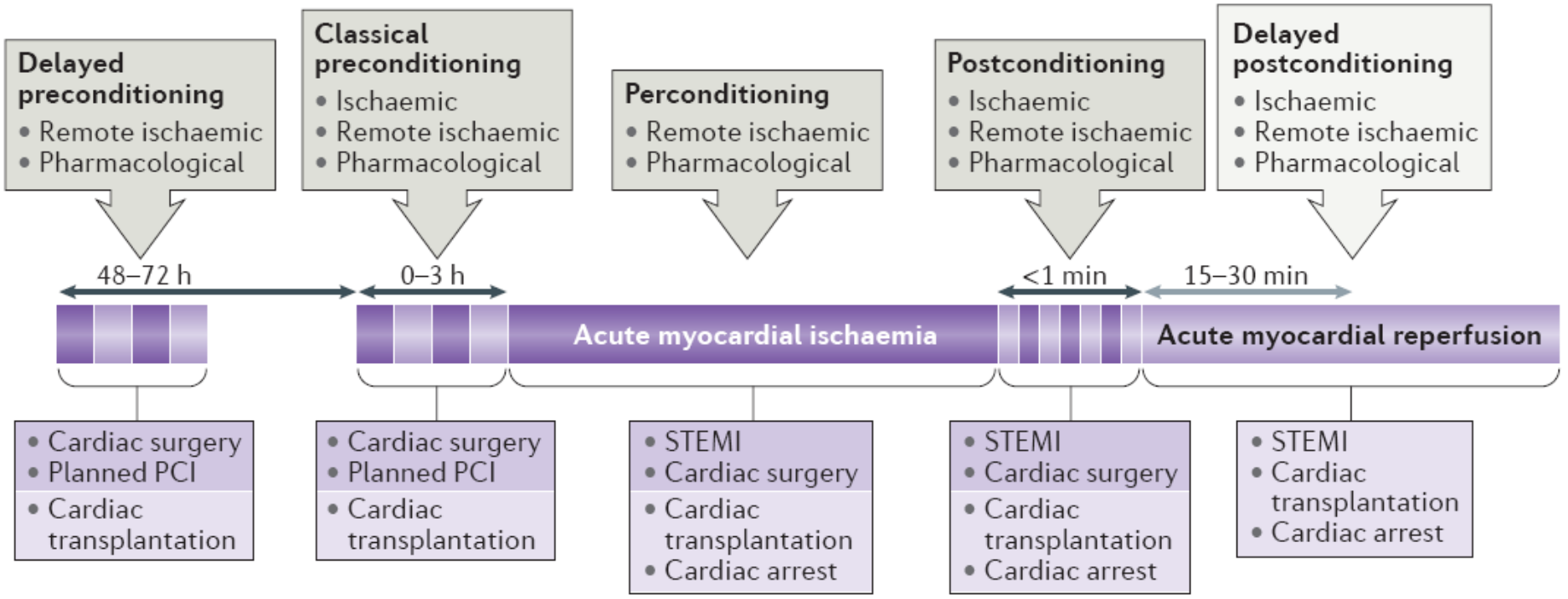
Ischemic conditioning to prevent I/R injury



***Clinical implication**

1) Ischemic *in situ* conditioning & post-conditioning

2) Pharmacological cardioprotection

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Clinical results of post-conditioning (STEMI)

Study	*n*	Patient selection	IPost protocol	Main outcome	Notes
Positive studies					
Staat *et al.* (2005)[49]	30	• LAD/RCA only • ≤6 h ischaemic time • TIMI 0 pre-PPCI • TIMI 2–3 post-PPCI • No collaterals • No angina in 48 h	• 4 × 1 min inflations and deflations of angioplasty balloon upstream of stent • Direct stenting	• 36% reduction in MI size (72 h AUC CK) • Better blush grade	• First clinical study to translate IPost into clinical setting
Ma *et al.* (2006)[51]	94	• All STEMI • ≤12 h ischaemic time • TIMI 3 post-PPCI	• 3 × 0.5 min inflations and deflations of angioplasty balloon	• 27% and 32% reductions in MI size (peak CK and CK–MB) • Better TIMI flow, WMSI, and endothelial function • Less malondialdehyde	• This study showed an alternative IPost protocol to be effective
Yang *et al.* (2007)[52]	41	• All STEMI • ≤12 h ischaemic time TIMI 0–1 pre-PPCI • No collaterals	• 3 × 0.5 min inflations and deflations of angioplasty balloon	• 27% reduction in MI size (72 h AUC CK) • 27% reduction in MI size (SPECT at 1 week)	• First clinical study to demonstrate MI size reduction on SPECT
Thibault *et al.* (2008)[53]	38	• LAD/RCA only • ≤6 h ischaemic time • TIMI 0 pre-PPCI • TIMI 2–3 post-PPCI • No collaterals • No angina in 48 h	• 4 × 1 min inflations and deflations of angioplasty balloon upstream of stent • Direct stenting	• 40% and 47% reductions in MI size (72 h AUC CK and troponin I) • 39% reduction in MI size (SPECT at 6 months) • 7% increase in LVEF (echo at 1 year)	• First clinical study to demonstrate long-term benefit with IPost
Lonborg *et al.* (2010)[54]	118	• All STEMI • ≤12 h ischaemic time • TIMI 0–1 pre-PPCI • TIMI 3 post-PPCI	• 4 × 0.5 min inflations and deflations of angioplasty balloon within the stent	• 31% increase in myocardial salvage ratio • 19% relative reduction in MI size (MRI at 3 months) • 41% reduction in patients developing heart failure	• First clinical study to demonstrate MI size reduction on MRI • Largest positive study to date

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Clinical results of post-conditioning (STEMI)

Study	*n*	Patient selection	IPost protocol	Main outcome	Notes
Neutral or negative studies					
Dwyer *et al.* (2013)[161]	102	• All STEMI • <6 h ischaemic time • TIMI 0–1 pre-PPCI • No collaterals	• 4 × 0.5 min inflations and deflations of angioplasty balloon at site of lesion	• No difference in myocardial salvage or MI size (MRI at day 3)	• First neutral study using an alternative IPost protocol
Hahn *et al.* (2014) POST[61]	700	• All STEMI • <12 h ischaemic time • TIMI 0–1 pre-PPCI	• 4 × 1 min inflations and deflations of angioplasty balloon at site of lesion	• No difference in ST-segment resolution, myocardial blush grade, peak CK–MB levels or MACE (death, MI, severe heart failure, or stent thrombosis) • No difference in MI size or myocardial salvage (MRI at day 3) in substudy of 111 patients[162]	• Largest and first multicentre study
Eitel *et al.* (2015) LIPSIA CONDITIONING[144]	333	• All STEMI	• 4 × 1 min inflations and deflations of angioplasty balloon at site of lesion versus control	• No difference in MI size, myocardial salvage (MRI at day 3), or MACE at 6 months	• Improved myocardial salvage when IPost combined with RIC
Ongoing studies					
DANAMI 3[68]	1,252	• All STEMI • <12 h ischaemic time • TIMI 0–1 pre-PPCI	• 4 × 0.5 min inflations and deflations of angioplasty balloon at site of lesion	• Primary outcome is all-cause death and heart failure at 2 years	• Recruitment complete • Currently in follow-up; results available early 2016

Hausenloy DJ, et al. Nat Rev Cardiol 2016

Clinical results of post-conditioning (STEMI)

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ACC 2016, DANish-iPOST (DANAMI 3-iPOST): DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: iPOST conditioning during primary PCI, Denmark

•Results: Ischemic post-conditioning after STEMI did not result in a reduction in death rates or HF hospitalization.

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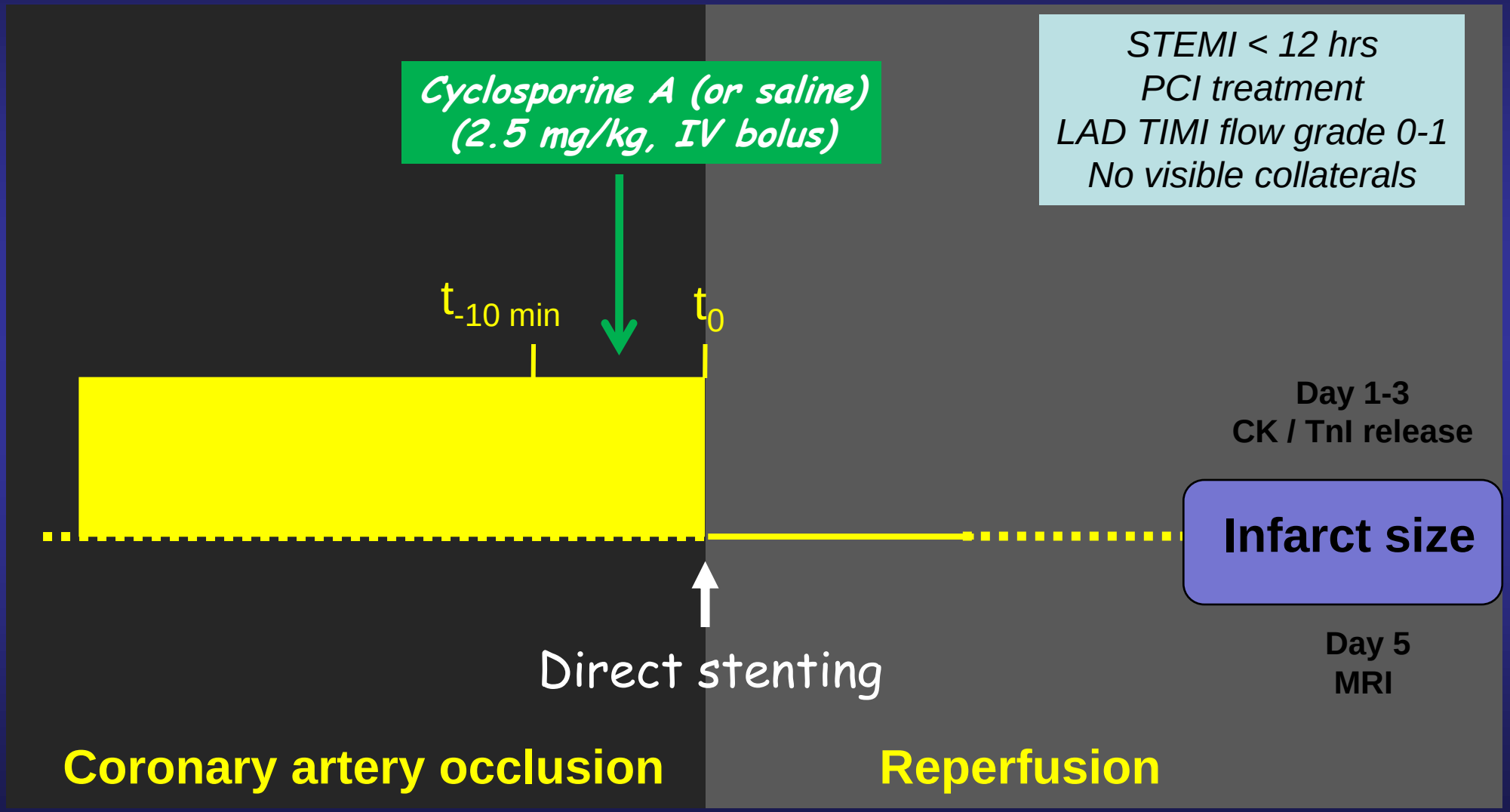
Piot et al. (NEJM 2008)

Objective: determine whether cyclosporine A can reduce infarct size in STEMI patients



Objective: dete … size in STEMI patients

STEMI < 12 hrs
PCI treatment
AD TIMI flow grade 0-1
No visible collaterals

Day 1-3
CK / TnI release

Infarct size

Day 5
MRI

Coronary ar… …on

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.

ABSTRACT

BACKGROUND

Experimental evidence suggests that cyclosporine, which inhibits the opening of mitochondrial permeability-transition pores, attenuates lethal myocardial injury that occurs at the time of reperfusion. In this pilot trial, we sought to determine whether the administration of cyclosporine at the time of percutaneous coronary intervention (PCI) would limit the size of the infarct during acute myocardial infarction.

METHODS

We randomly assigned 58 patients who presented with acute ST-elevation myocardial infarction to receive either an intravenous bolus of 2.5 mg of cyclosporine per kilogram of body weight (cyclosporine group) or normal saline (control group) immediately before undergoing PCI. Infarct size was assessed in all patients by measuring the release of creatine kinase and troponin I and in a subgroup of 27 patients by performing magnetic resonance imaging (MRI) on day 5 after infarction.

RESULTS

The cyclosporine and control groups were similar with respect to ischemia time, the size of the area at risk, and the ejection fraction before PCI. The release of creatine kinase was significantly reduced in the cyclosporine group as compared with the control group (P=0.04). The release of troponin I was not significantly reduced (P=0.15). On day 5, the absolute mass of the area of hyperenhancement (i.e., infarcted tissue) on MRI was significantly reduced in the cyclosporine group as compared with the control group, with a median of 37 g (interquartile range, 21 to 51) versus 46 g (interquartile range, 20 to 65; P=0.04). No adverse effects of cyclosporine administration were detected.

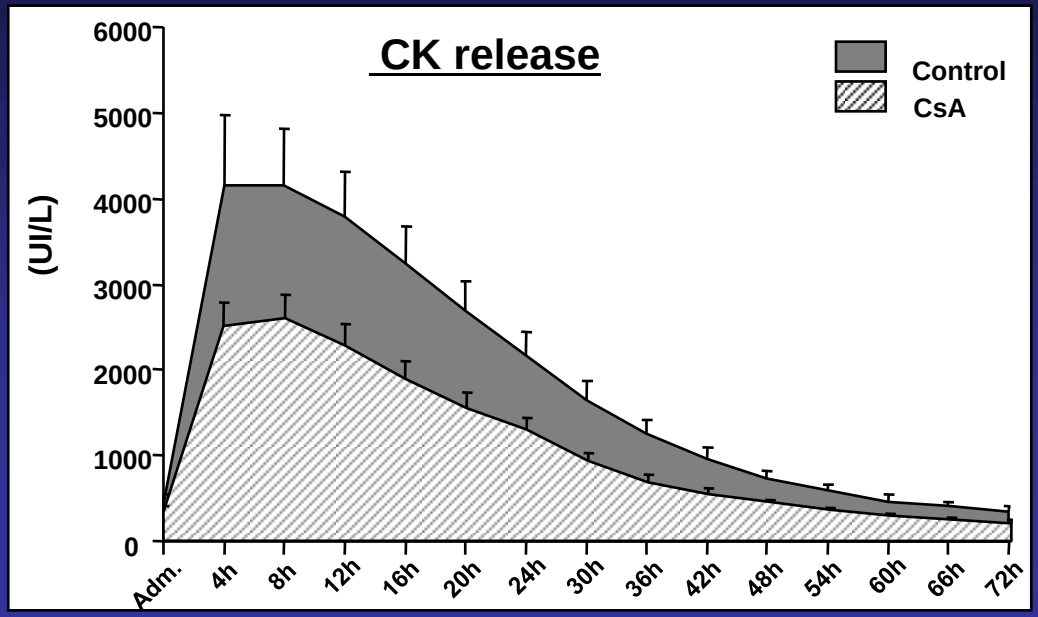
CONCLUSIONS

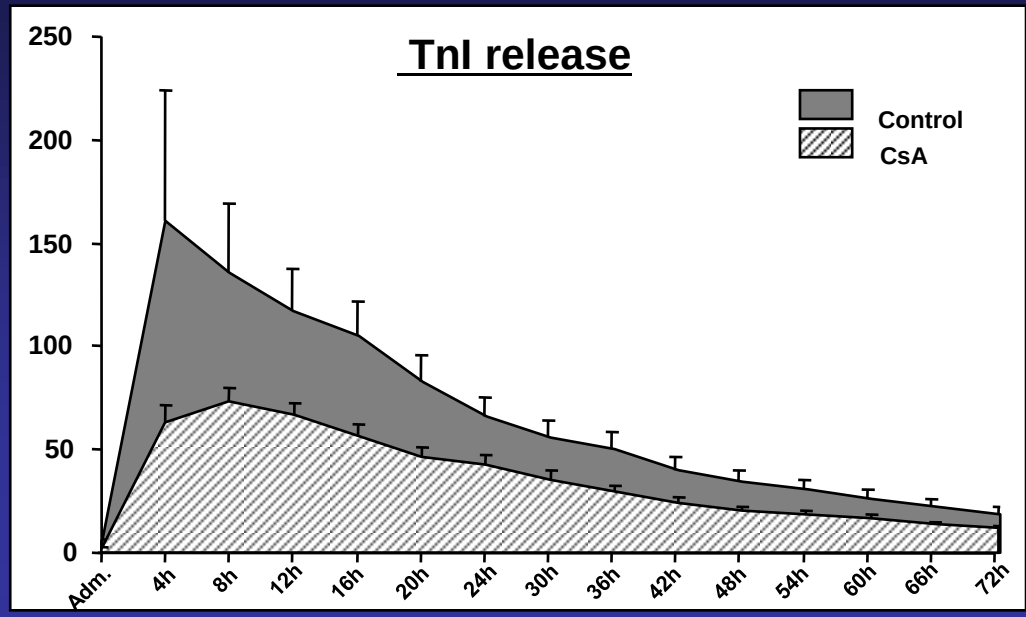
In our small, pilot trial, administration of cyclosporine at the time of reperfusion was associated with a smaller infarct by some measures than that seen with placebo. These data are preliminary and require confirmation in a larger clinical trial.

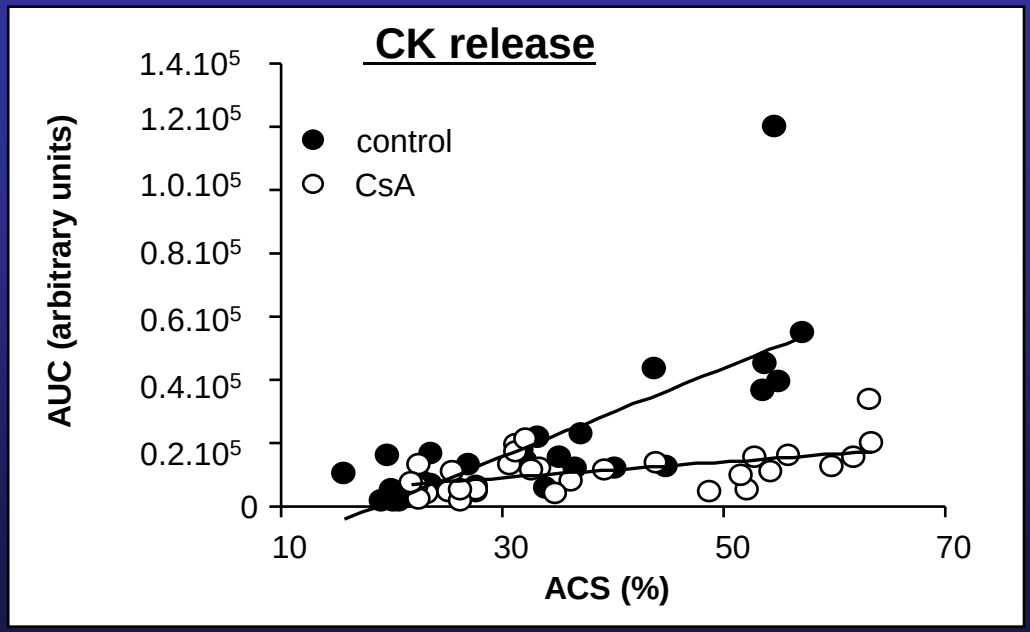
From Hôpital Arnaud de Villeneuve, Montpellier (C.P., T.T.C., C.M., F.R., C.S., G.G.); Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon (P.C., P.S., H.T., G.R., N.M., E.B., D.A., G.F., X.A.-F., D.R., G.K., G.D., M.O.); Service de Cardiologie, Mulhouse (R.E., J.-P.M.); and INSERM Unité 886, Lyon (H.T., G.R., D.A., G.F., G.D., M.O.) — all in France. Address reprint requests to Dr. Ovize at Hôpital L. Pradel, Hospices Civils de Lyon, 59, Blvd. Pinel, 69394 Lyon CEDEX 03, France, or at ovize@sante.univ-lyon1.fr.

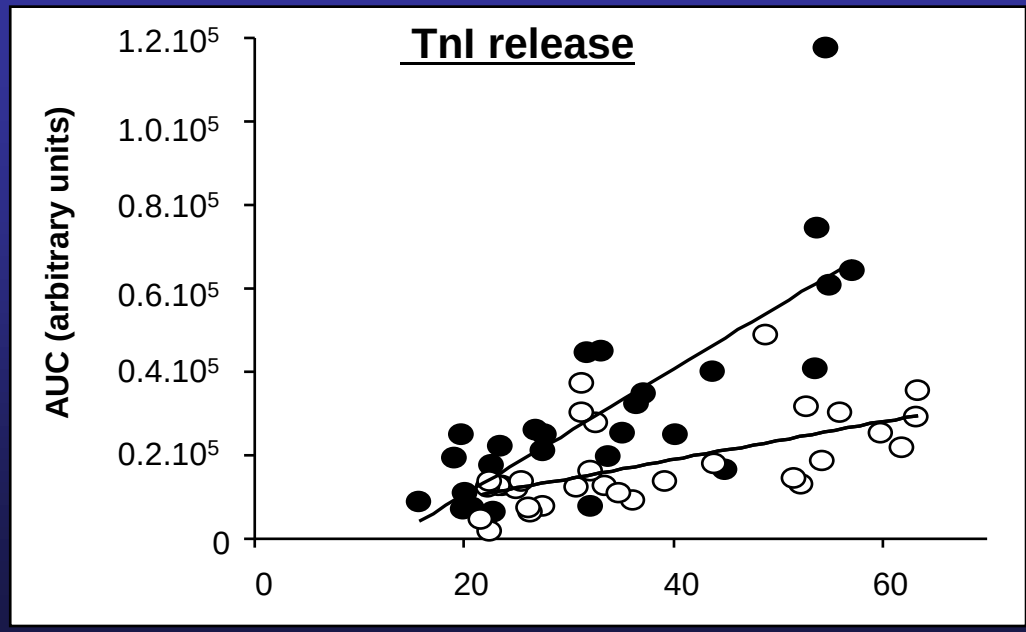
N Engl J Med 2008;359:473-81.

Reduction of cardiac enzymes release by cyclosporine A
Piot et al. NEJM 2008









Clinical results of pharmacological cardioprotection

Cyclosporine before PCI in Patients with Acute Myocardial Infarction

T.-T. Cung, O. Morel, G. Cayla, G. Rioufol, D. Garcia-Dorado, D. Angoulvant, E. Bonnefoy-Cudraz, P. Guérin, M. Elbaz, N. Delarche, P. Coste, G. Vanzetto, M. Metge, J.-F. Aupetit, B. Jouve, P. Motreff, C. Tron, J.-N. Labeque, P.G. Steg, Y. Cottin, G. Range, J. Clerc, M.J. Claeys, P. Coussement, F. Prunier, F. Moulin, O. Roth, L. Belle, P. Dubois, P. Barragan, M. Gilard, C. Piot, P. Colin, F. De Poli, M.-C. Morice, O. Ider, J.-L. Dubois-Randé, T. Unterseeh, H. Le Breton, T. Béard, D. Blanchard, G. Grollier, V. Malquarti, P. Staat, A. Sudre, E. Elmer, M.J. Hansson, C. Bergerot, I. Boussaha, C. Jossan, G. Derumeaux, N. Mewton, and M. Ovize

970 patients: acute anterior ST-segment elevation myocardial infarction (STEMI) who were undergoing PCI within 12 hours after symptom onset
*CicloMulsion: NeuroVive Pharmaceutical, Sweden

CONCLUSIONS

In patients with anterior STEMI who had been referred for primary PCI, intravenous cyclosporine did not result in better clinical outcomes than those with placebo and did not prevent adverse left ventricular remodeling at 1 year. (Funded by the French Ministry of Health and NeuroVive Pharmaceutical; CIRCUS ClinicalTrials.gov number, NCT01502774; EudraCT number, 2009-013713-99.)

Cyclosporine A in Reperfused Myocardial Infarction

The Multicenter, Controlled, Open-Label CYCLE Trial

Filippo Ottani, MD,[a] Roberto Latini, MD,[b] Lidia Staszewsky, MD,[b] Luigi La Vecchia, MD,[c] Nicola Locuratolo, MD,[d] Marco Sicuro, MD,[e] Serge Masson, PhD,[b] Simona Barlera, MS,[b] Valentina Milani, PhD,[b] Mario Lombardi, MD,[f] Alessandra Costalunga, MD,[g] Nadia Mollichelli, MD,[h] Andrea Santarelli, MD,[i] Nicoletta De Cesare, MD,[j] Paolo Sganzerla, MD,[k] Alberto Boi, MD,[l] Aldo Pietro Maggioni, MD,[m] Ugo Limbruno, MD,[n] on behalf of the CYCLE Investigators

410 patients: large ST-segment elevation MI within 6 h of symptom onset
*CsA (Sandimmune): Novartis, Switzerland

CONCLUSIONS In the CYCLE (CYCLosporinE A in Reperfused Acute Myocardial Infarction) trial, a single intravenous CsA bolus just before primary percutaneous coronary intervention had no effect on ST-segment resolution or hs-cTnT, and did not improve clinical outcomes or LV remodeling up to 6 months. (CYCLosporinE A in Reperfused Acute Myocardial Infarction [CYCLE]; NCT01650662; EudraCT number 2011-002876-18) (J Am Coll Cardiol 2016;67:365-74)

Targeting Myocardial IR Injury — The Search Continues

Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Results of Exenatide Myocardial Protection in Revascularization Study

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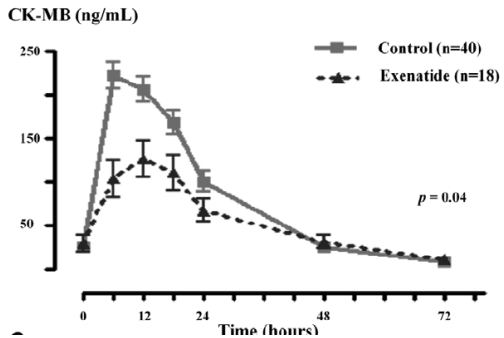
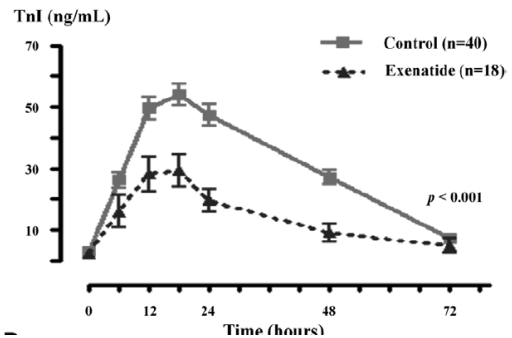
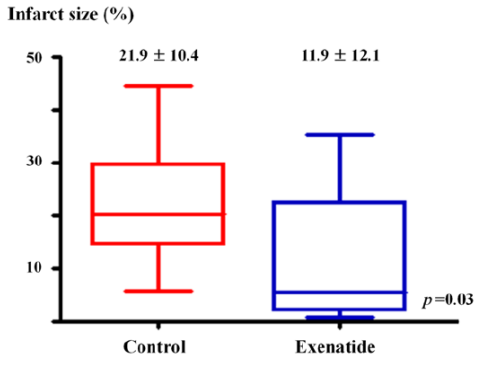
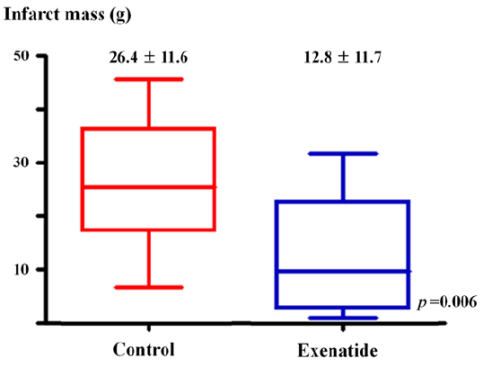
58 patients: acute STEMI within the 12 h of the onset of symptoms
*exenatide: 10 μg SC and IV bolus 10 μg injection of BYETTA® (Amylin-Lilly) 5 min before the onset of reperfusion. In addition, 10 μg SC bid on the following 2 days.

Conclusions—In patients with ST-segment–elevation myocardial infarction, adjunctive exenatide therapy with primary percutaneous coronary intervention was associated with reduction of infarct size and improvement of subclinical left ventricular function. **(*Arterioscler Thromb Vasc Biol*. 2013;33:2252-2260.)**







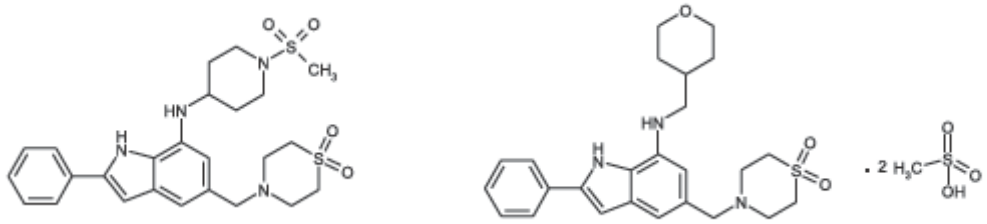


Targeting Myocardial IR Injury — The Search Continues

Necrosis inhibitor, NecroX ?

NecroX-7; from LG life sciences (SH Kim, PhD)

Derivative and combination of products



Anti-necrotic effect by some mechanisms

via 1) Strong antioxidant

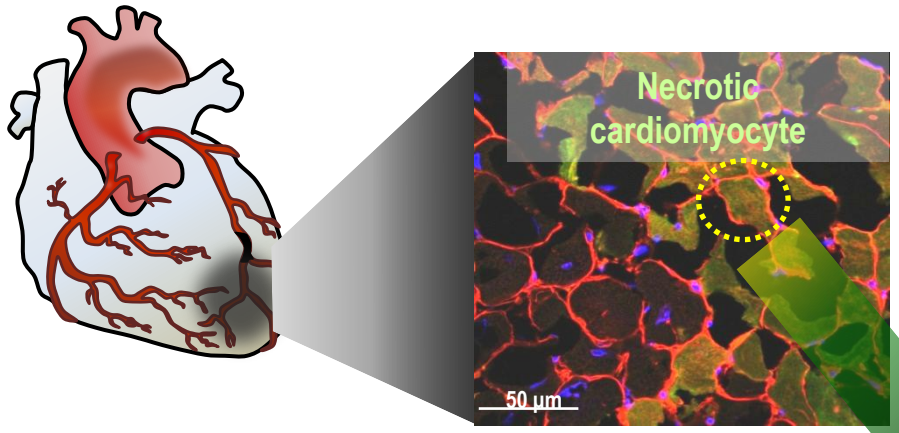
2) Inhibition of HMGB1

3) Mitochondrial ROS and $ONOO^-$ scavenger

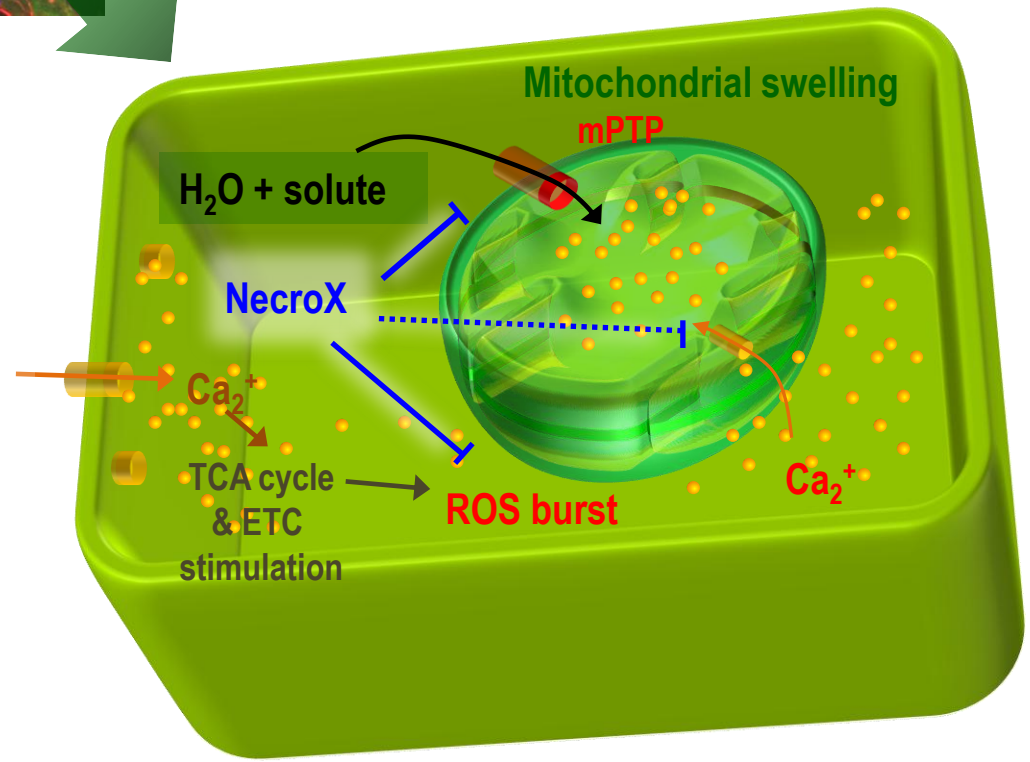
Well-known the effect on hepatic ischemia/reperfusion injury

Transplant Proc 2010

Mechanism of necrosis inhibitor, NecroX



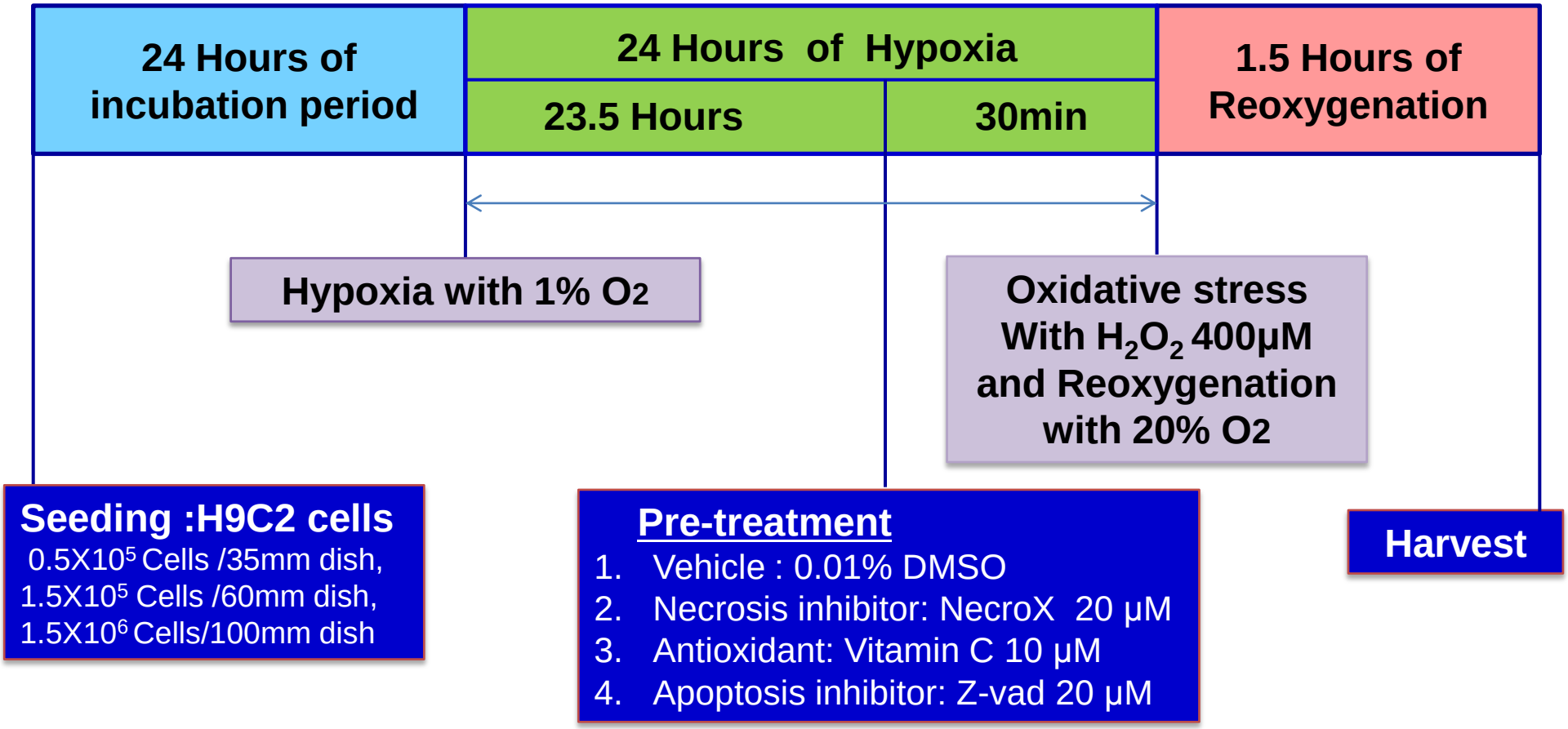
Necrotic cardiomyocyte



Necrosis inhibitor

In vitro Design

Hypoxia-Oxidative stress/Reoxygenation (**H-O/R**) model using H9C2 cell (myoblast cell line)



Measurement of mitochondrial Ca^{2+} influx

Hypoxia 24h + Oxidative stress with H_2O_2

Vehicle

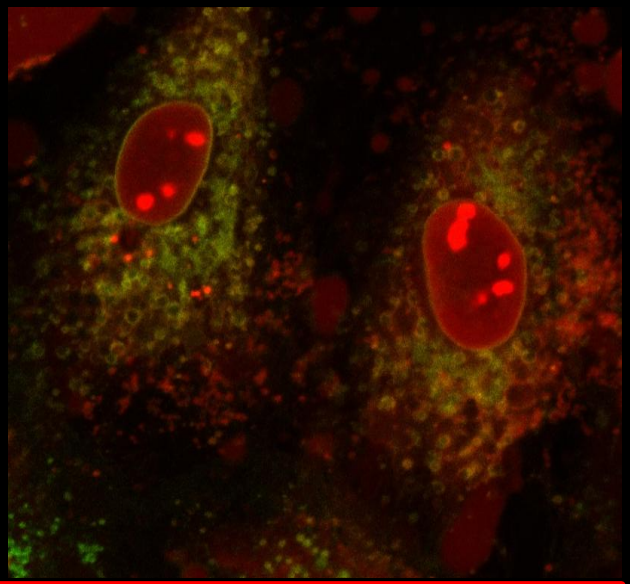
NecroX

Time (minutes)

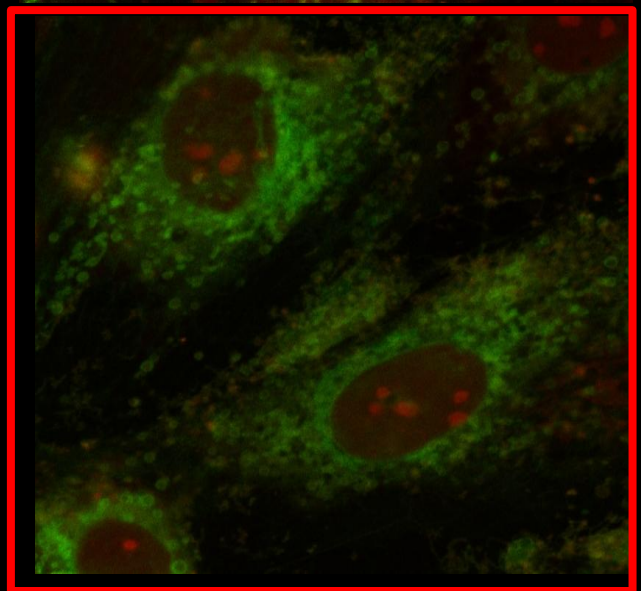
Mitotracker : mitochondria

Rhod-2 : $Ca2^{+}$ influx

Vehicle treated group showed prominent calcium influx (red stain) in the swollen mitochondria via mPTP opening



Necrosis Inhibitor revealed protective effect on mPTP opening under I/RI

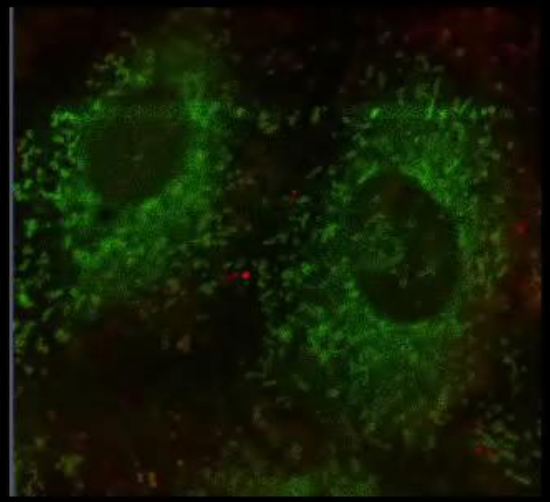


Measurement of mitochondrial Ca^{2+} influx

Under hypoxia and oxidative stress condition

Vehicle (3~5 minutes)

[Vehicle-treated H9C2 cells]

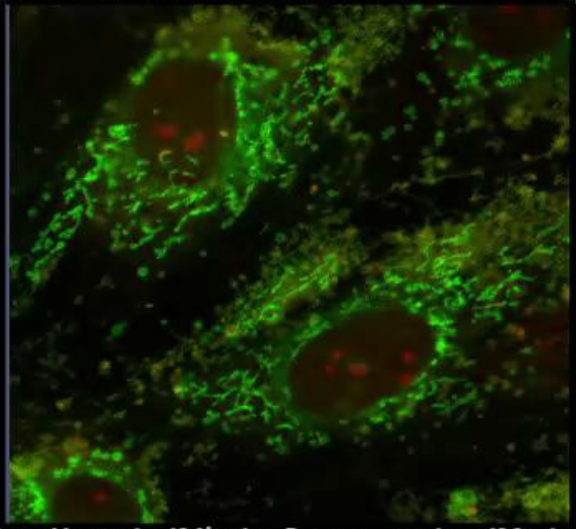


* Condition: Hypoxia (24hrs) - Reoxygenation (90mins)
* Red (Rhod-2 fluorescence) : free Ca2+ level
* Green (Mitotracker) : mitochondrial shape

H9C2 cells pretreated with vehicle (DMSO) exhibiting rapid increase in Ca2+ influx and mitochondrial swelling.

Necrosis Inhibitor (over 30minutes)

[NecX-treated H9C2 cells]

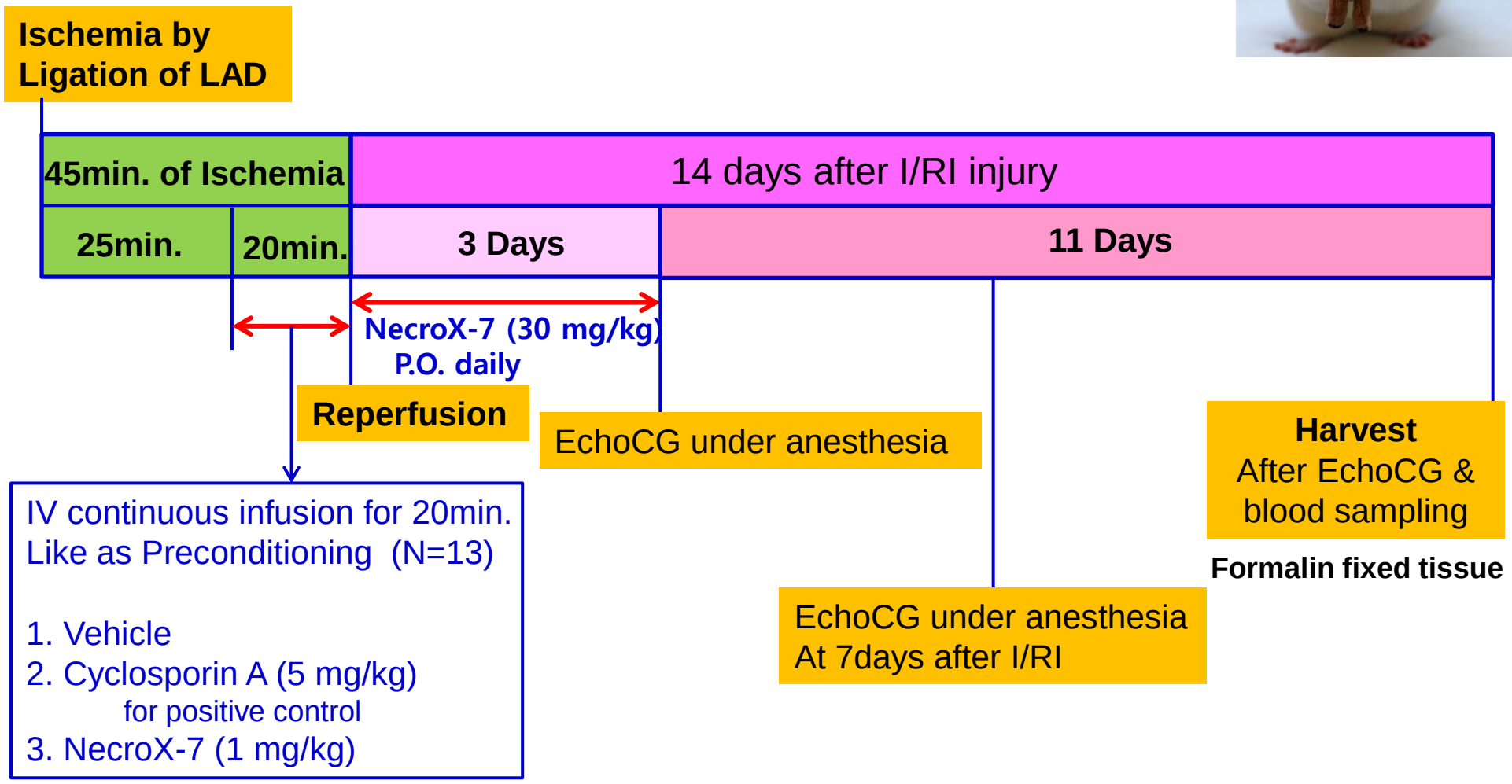


* Condition: Hypoxia (24hrs) - Reoxygenation (90mins)
* Red (Rhod-2 fluorescence): free Ca2+ level
* Green (Mitotracker): mitochondrial shape

H9C2 cells pretreated with necrosis inhibitor (NecX) showing minimal increase in Ca2+ influx and preserved mitochondrial shapes.

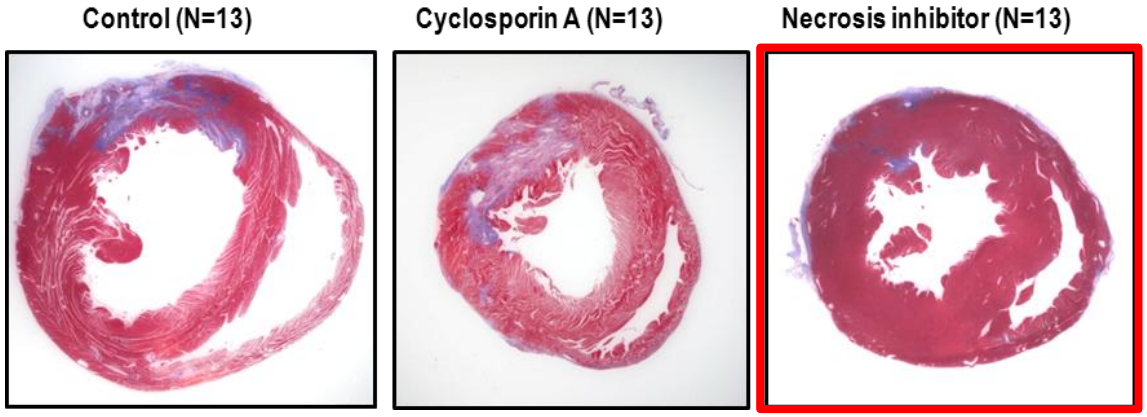
Necrosis inhibitor

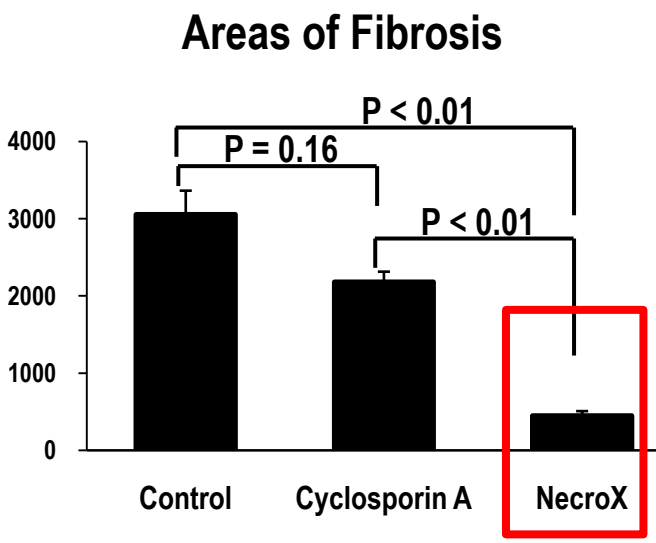
In vivo Design

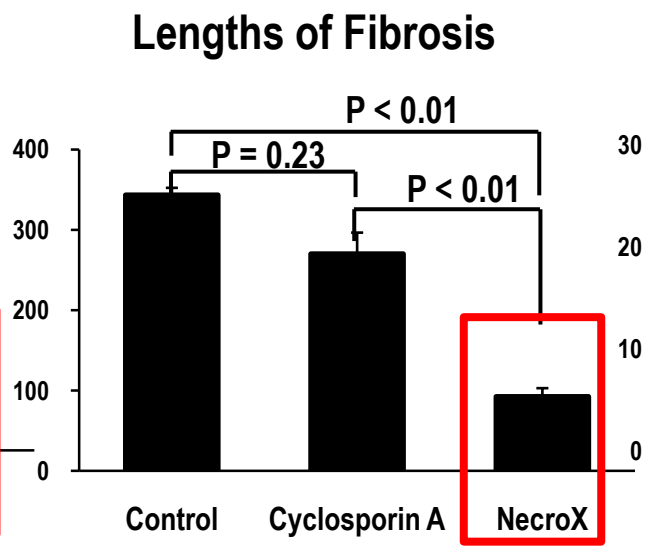


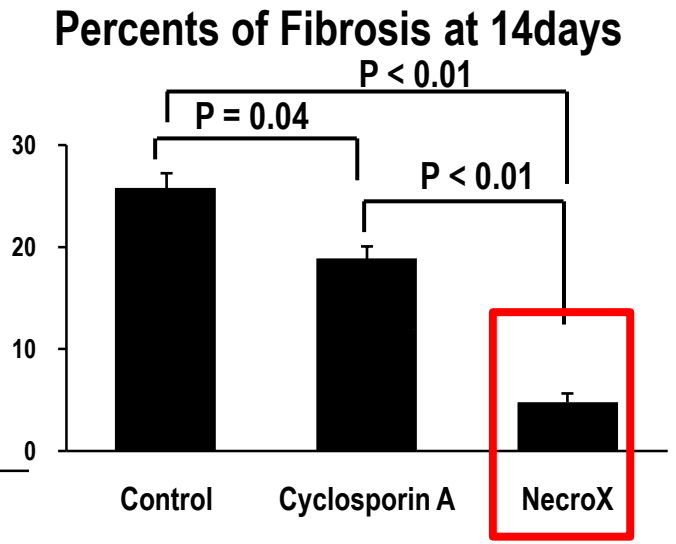
Necrosis inhibitor

Day 14 harvested heart

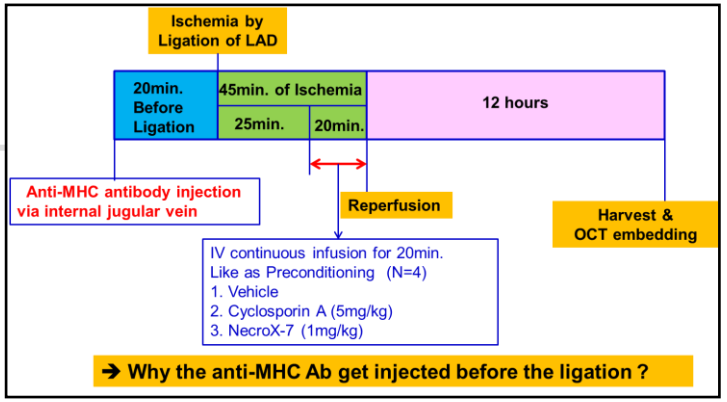




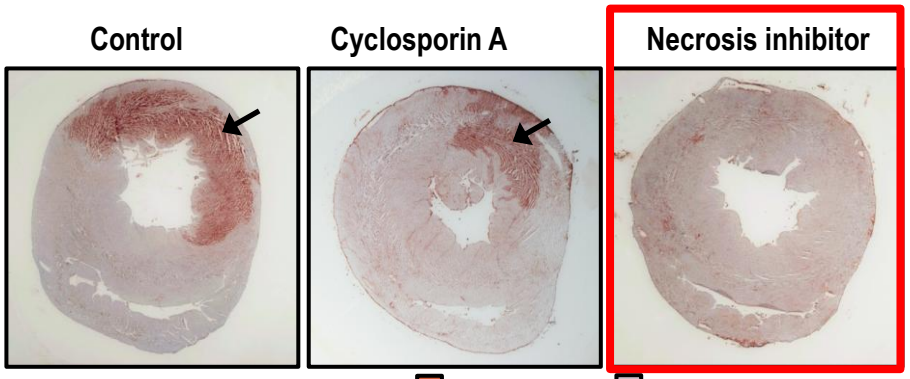




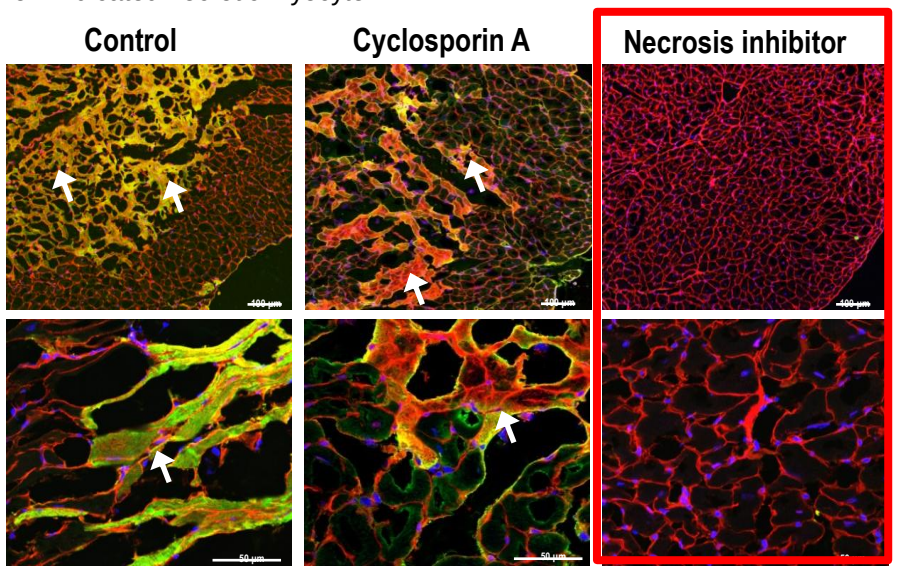
Necrosis inhibitor



Quantification for Necrosis

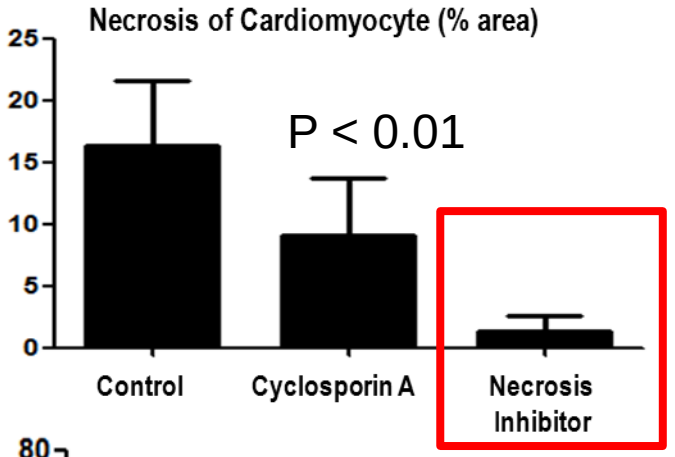


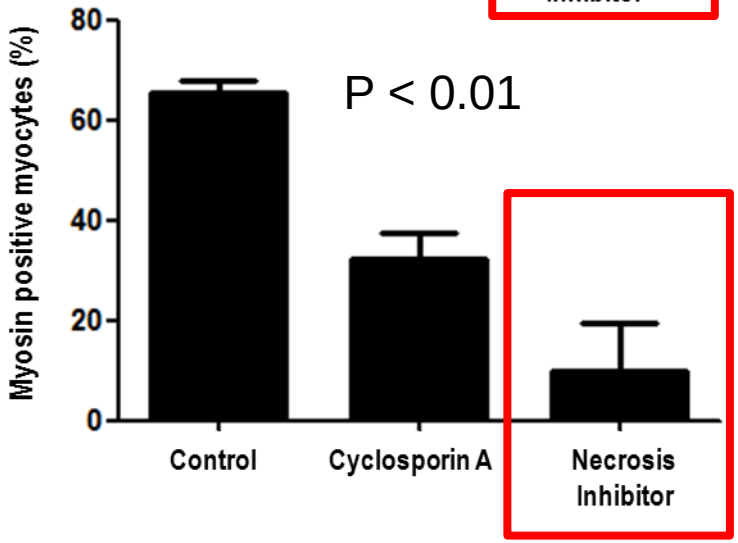
Black arrow indicated necrotic myocyte. Necrotic zone Non-necrotic zone



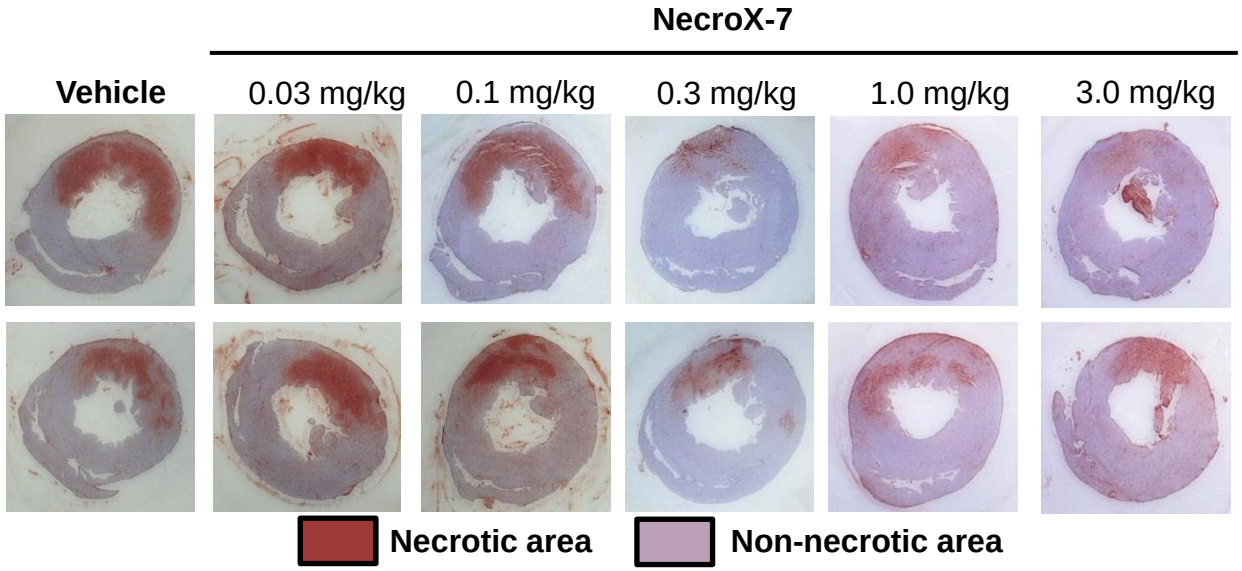
Necrotic myocyte (MHC+) WGA (Sarcolemma) Nucleus

White arrow indicated necrotic myocyte.

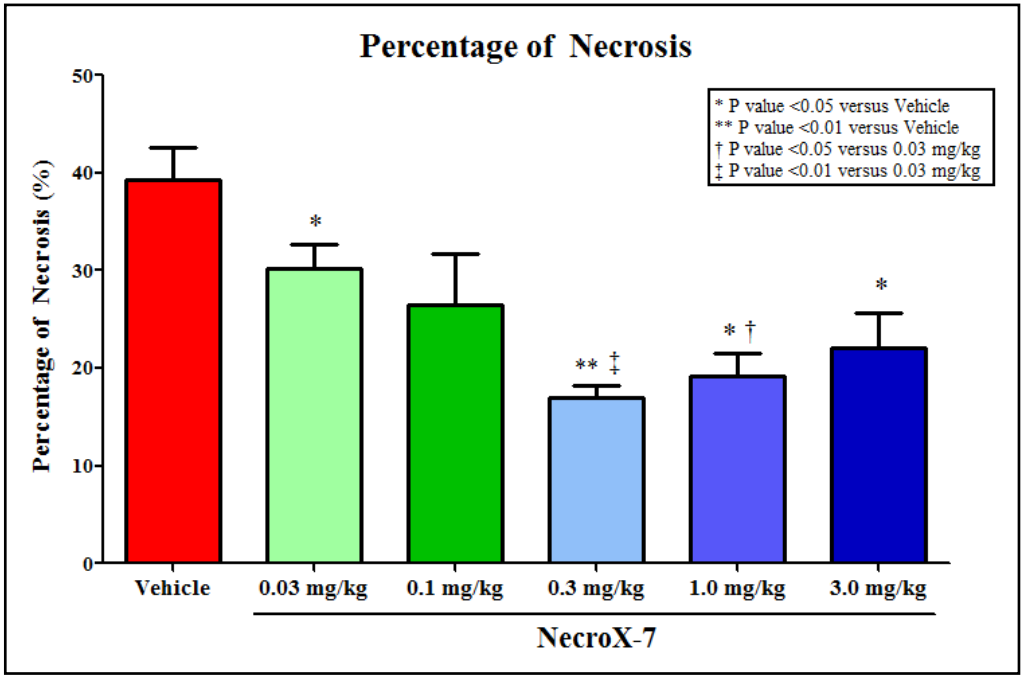




Necrosis inhibitor: dose finding preclinical study



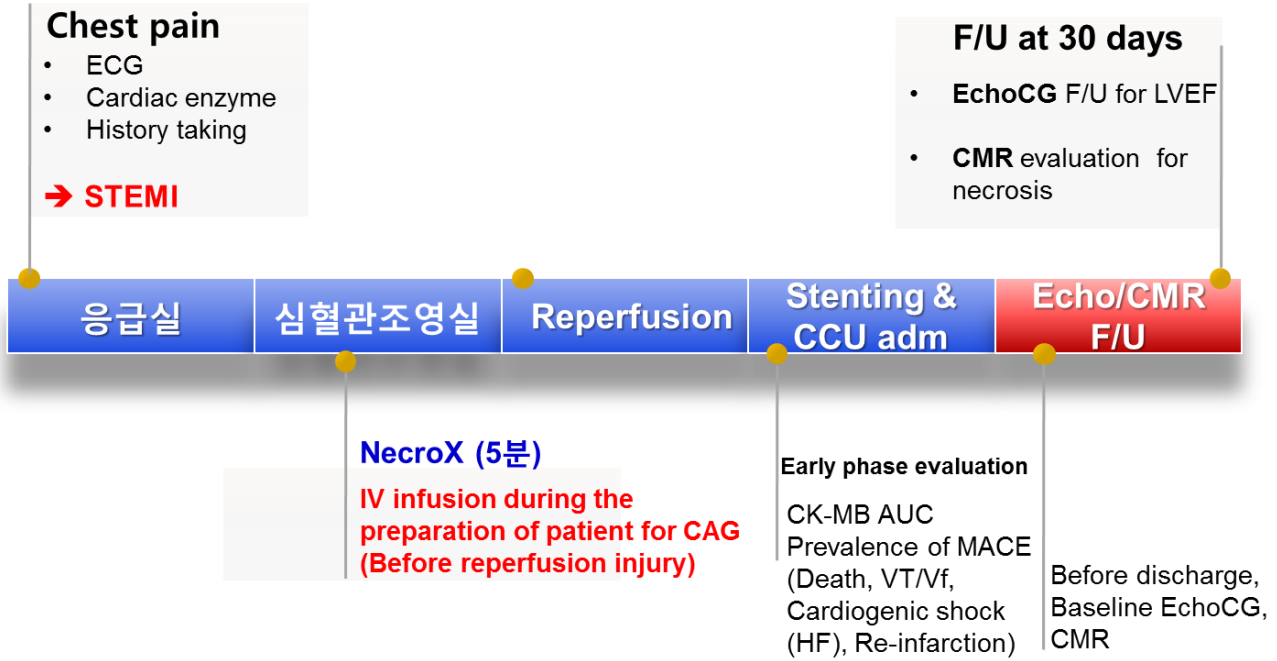
- NecroX prevented myocardial necrosis from I/R injury.
- The minimal effective dose (MED) in Rat MI/R model was 0.3 mg/kg.



Necrosis inhibitor: clinical trials

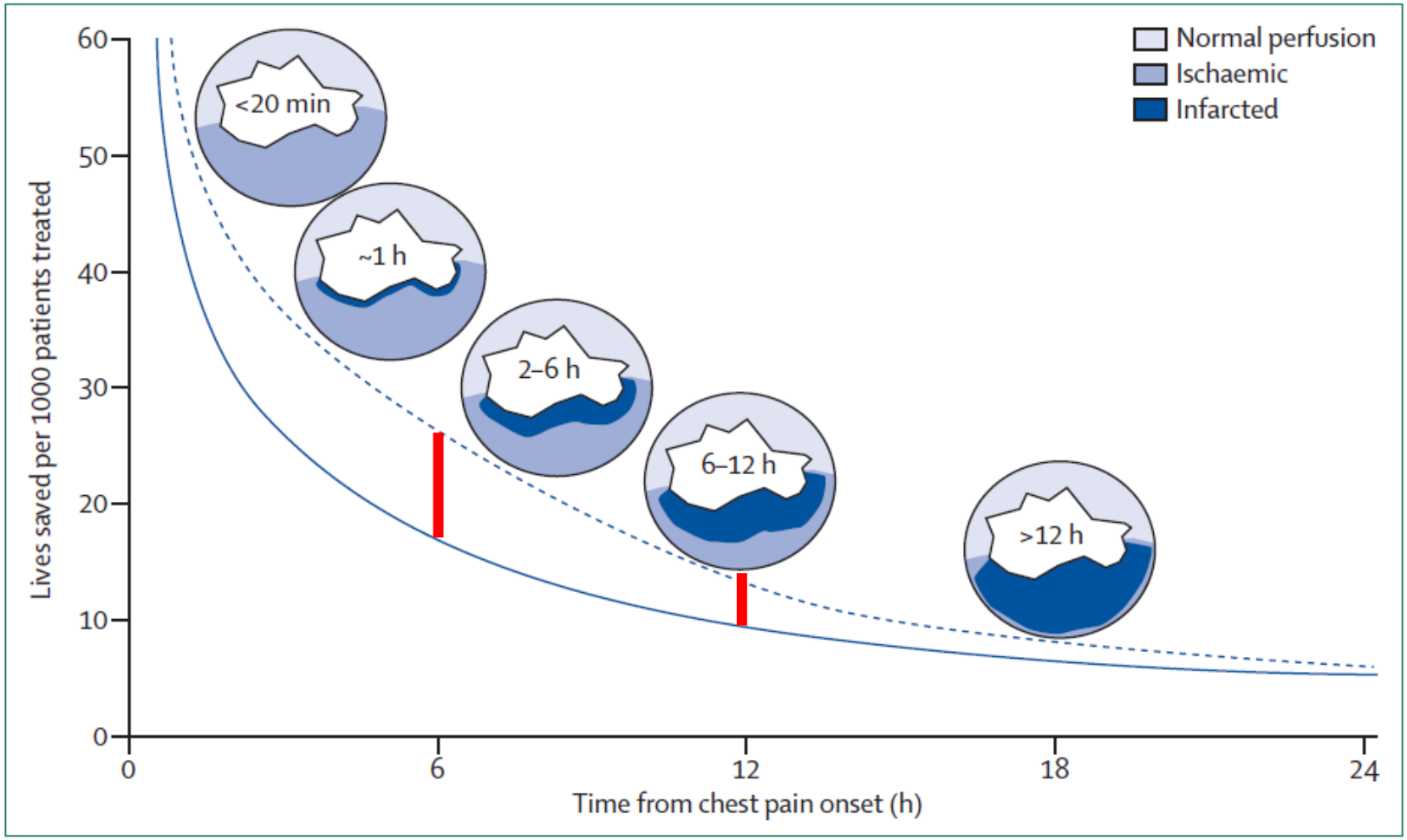
Phase 1. 건강한 남성 피험자를 대상으로 LC28-0126의 안전성, 내약성 및 약동학적 특성을 평가하기 위한 용량군별 무작위배정, 이중눈가림, 위약대조, 단회투여, 단계적 증량 제 1상 임상시험

Phase 2a. ST분절 상승 심근경색(ST-segment Elevation Myocardial Infarction) 환자를 대상으로 경피적 관상동맥 중재술 (Percutaneous Coronary Intervention, PCI) 전, LC28-0126을 단회 정맥 주사 시 효능, 안전성 및 약동학적 특성을 평가하기 위한 다기관, 무작위 배정, 병행설계, 이중눈가림, 위약 대조, 임상 2상 시험



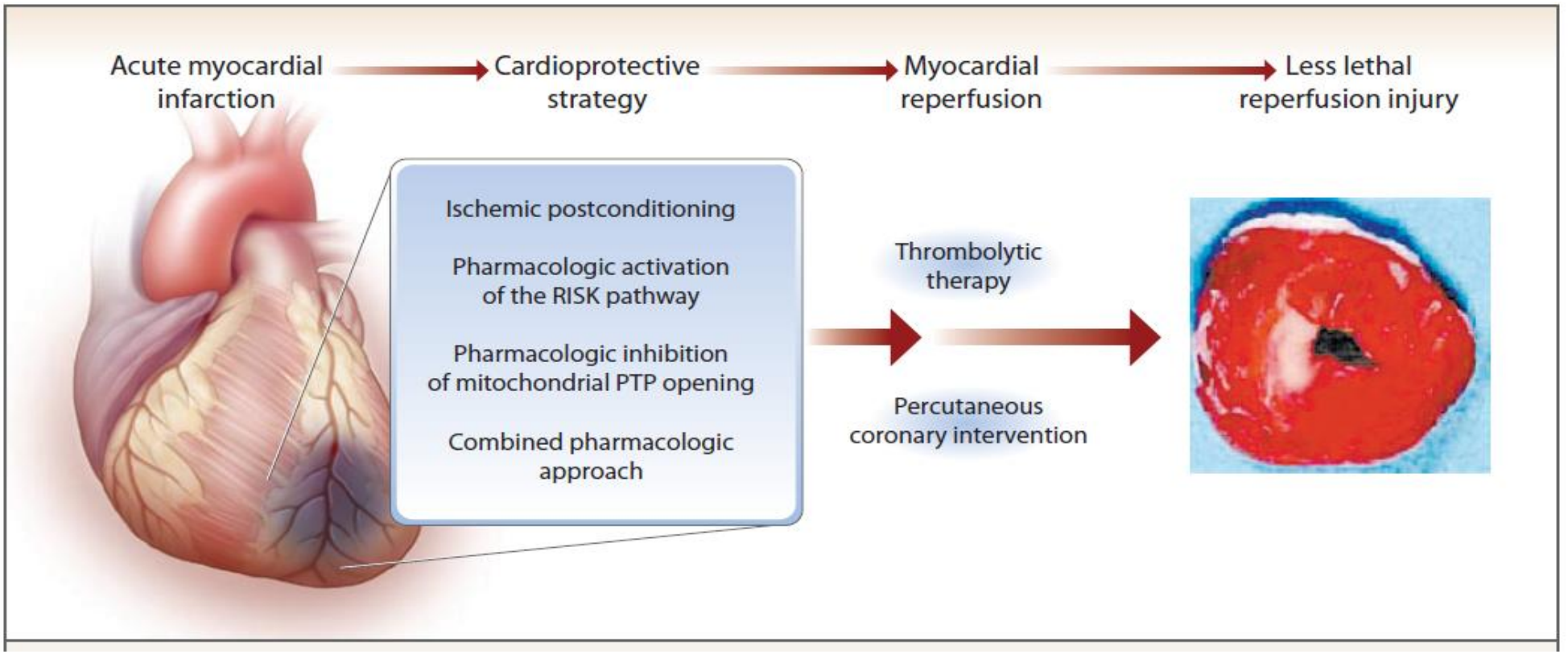
Phase 2b. ***Ongoing***

Benefit of Reperfusion & Prevention of IR injury



- Solid line: the benefit of reperfusion in terms of lives saved at 35 days
- Dotted line: relation between an effective cardioprotective intervention and reperfusion

Lancet. 2013;382:644–657



Cardio-protection *before* reperfusion

The mitochondrial PTP is a nonselective channel of the inner mitochondrial membrane. Opening the channel collapses the mitochondrial membrane potential and uncouples oxidative phosphorylation, resulting in ATP depletion and cell death.

During myocardial ischemia, the mitochondrial PTP remains closed, only to open within the first few minutes after myocardial reperfusion in response to mitochondrial Ca2+ overload, oxidative stress, restoration of a physiologic pH, and ATP depletion.
Therefore, the mitochondrial PTP is a critical determinant of lethal reperfusion injury, and as such it is an important new target for cardioprotection.

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Thank you for your attention

경청해 주셔서 감사합니다

Reperfusion Injury: How Can We Reduce It?

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