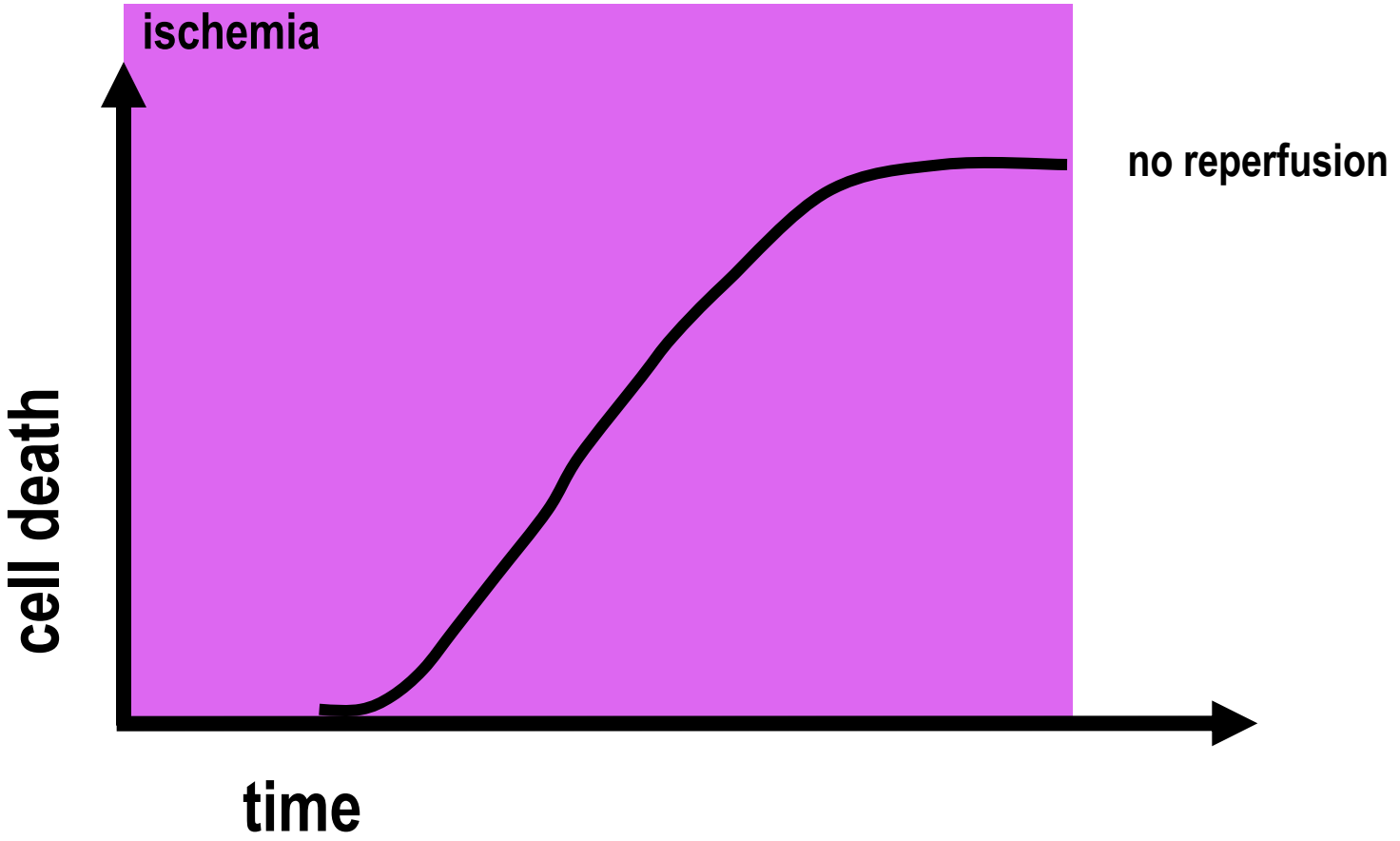
Basic Cardiovascular Science

Reperfusion injury in STEMI. Therapeutic opportunities

David Garcia-Dorado. Barcelona. Spain

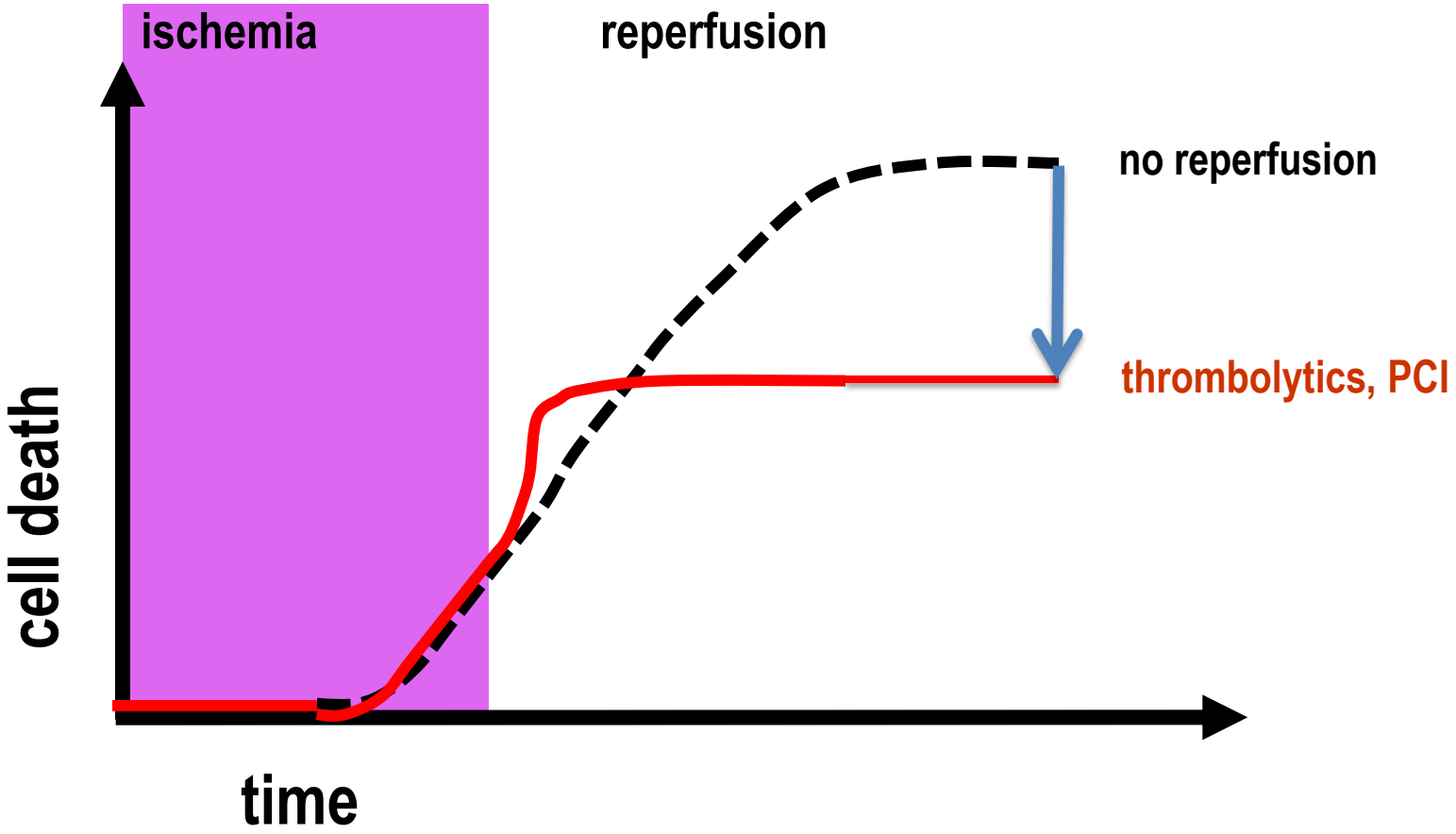
1. The problem
2. Reperfusion injury after acute coronary occlusion
3. Ischemic conditioning
4. Pharmacological approaches
5. Combination therapy
6. Future research

Progression of cell death secondary to acute coronary occlusion



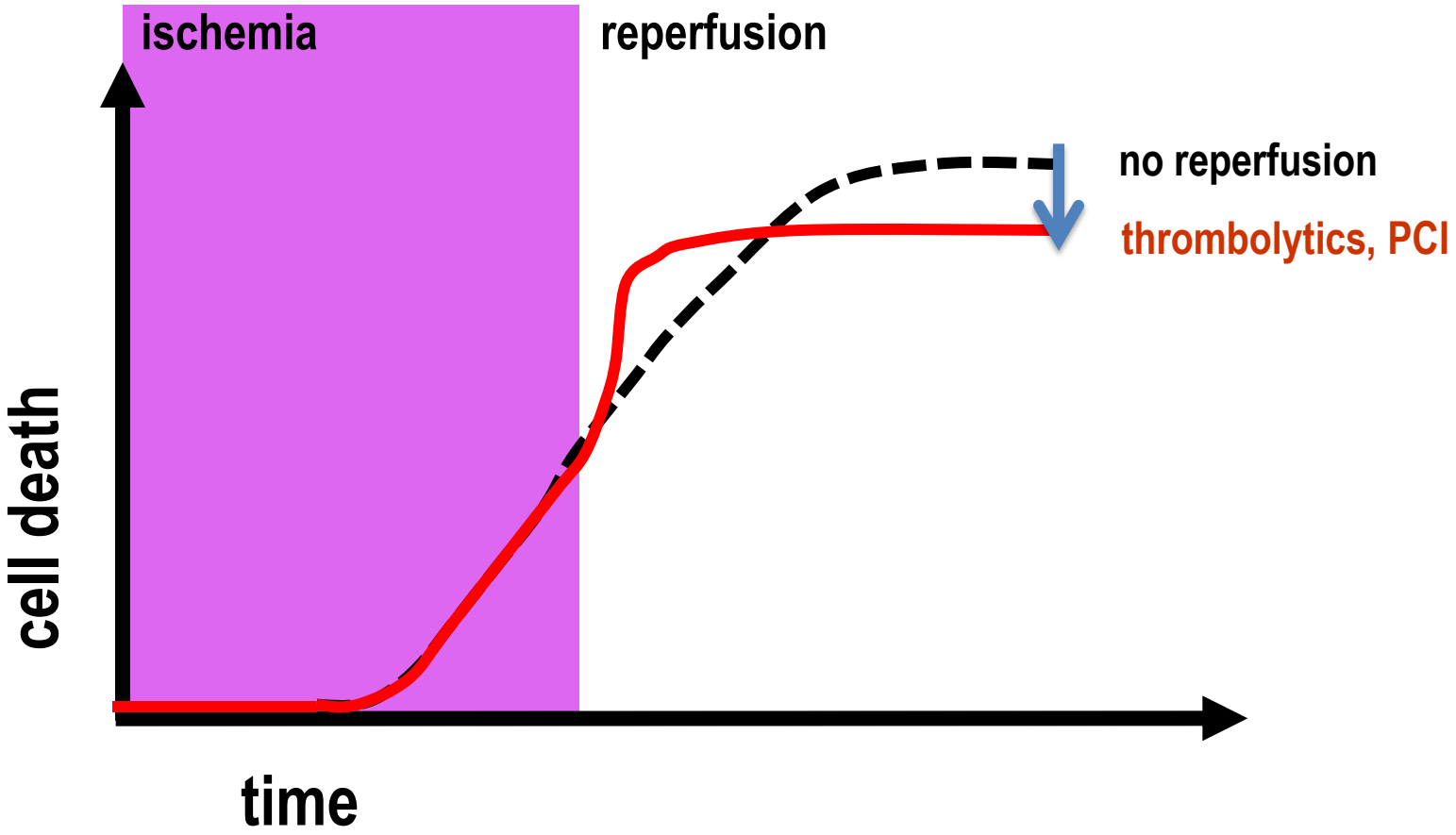
D. Garcia-Dorado, H.M. Piper / Cardiovascular Research 69 (2006) 1–

Progression of cell death secondary to acute coronary occlusion



D. Garcia-Dorado, H.M. Piper / Cardiovascular Research 69 (2006) 1–

Progression of cell death secondary to acute coronary occlusion



D. Garcia-Dorado, H.M. Piper / Cardiovascular Research 69 (2006) 1–

The importance of delaying reperfusion depends on previous duration of ischemia

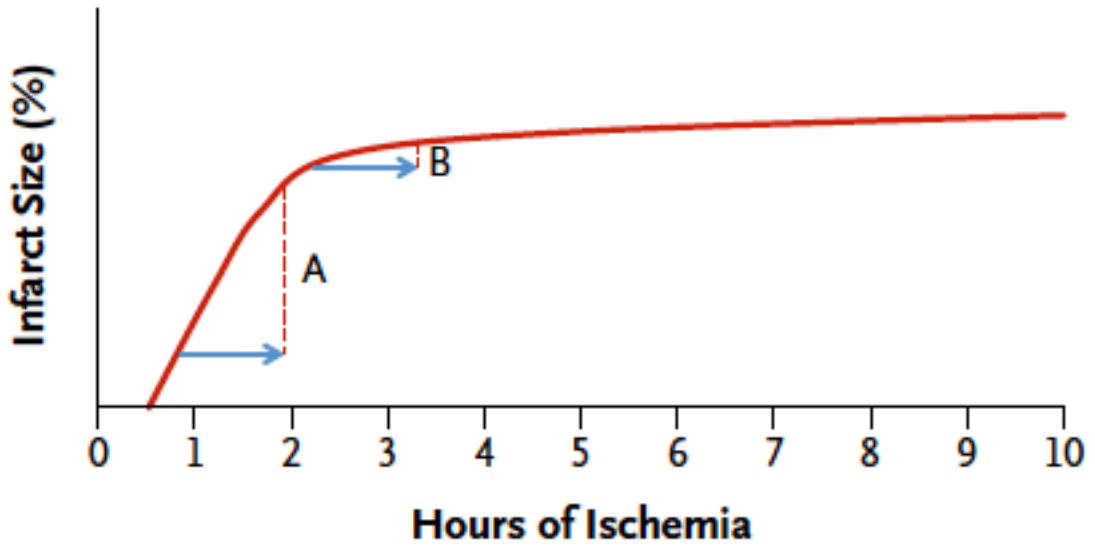
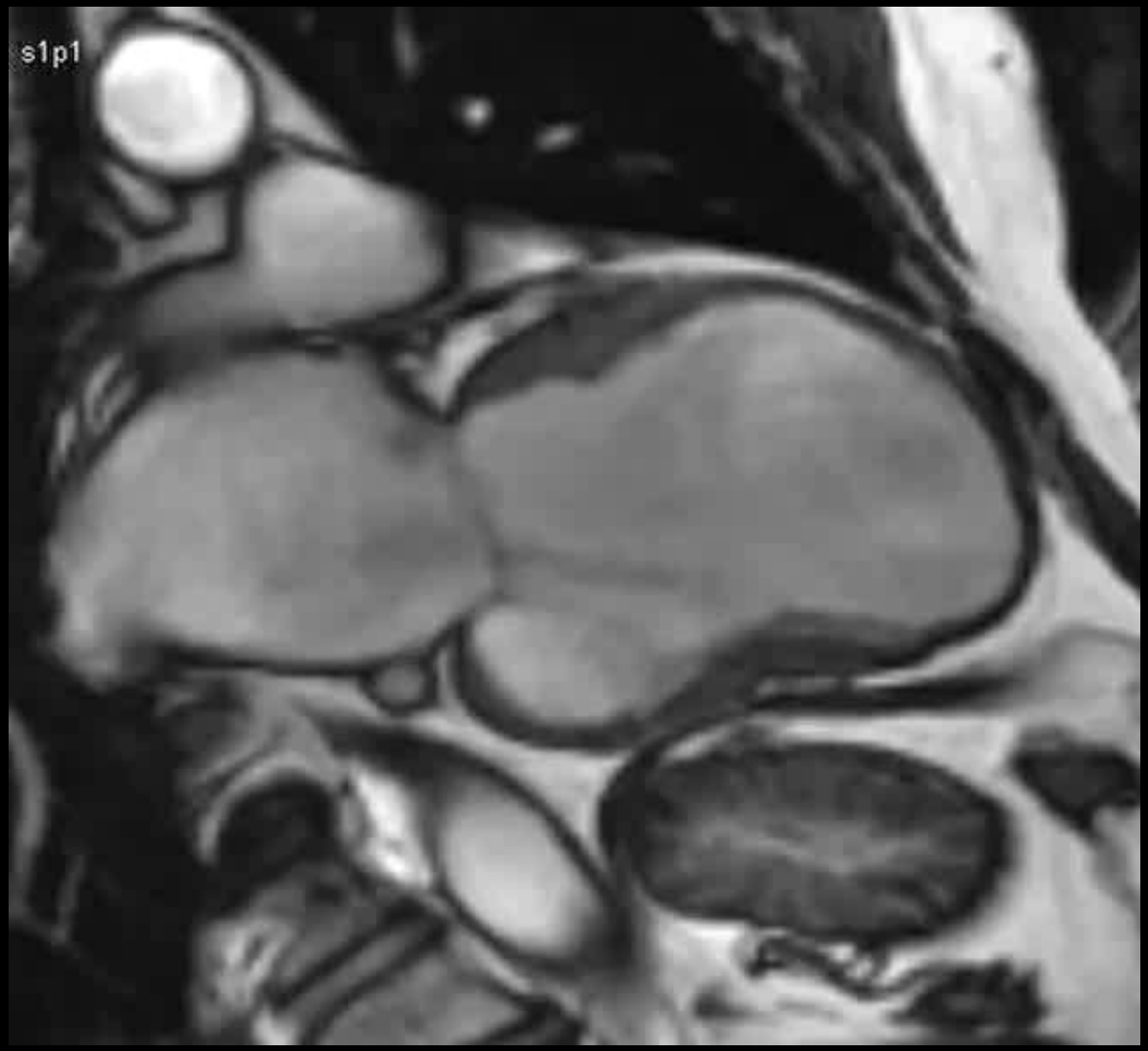


Figure 1. Duration of Ischemia and Infarct Size.

Shown is a typical relationship between the duration of ischemia and infarct size (as a percentage of the area at risk) in patients with STEMI, with a rapid phase of increase in size as reperfusion is delayed, followed by a plateau. The effect of a delay (arrow) on infarct size may be large (A) or small (B), depending on the total ischemic time.

Garcia-Dorado et al. N ENGL J MED 370;2 NEJM.ORG JANUARY 9, 2014


s1p1

1. The problem

- IHD is the leading cause of death (1.8 million/year world wide)
- Heart failure consumes 1 - 2% of health resources (60 billion € in Europe)
- STEMI remains the main responsible for both in the era of reperfusion

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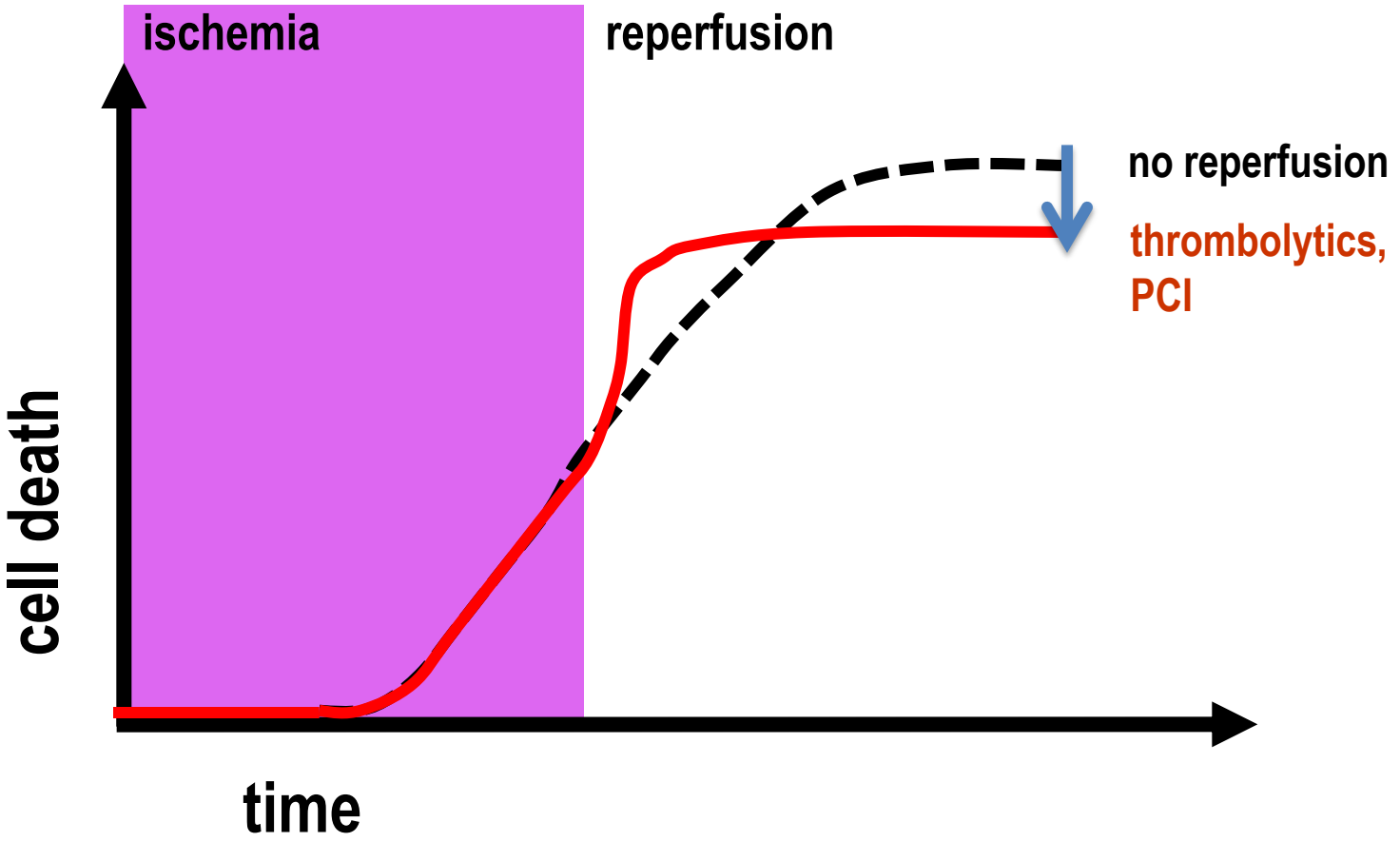
Myocardial reperfusion injury:
cell death preventable by interventions applied upon reperfusion *



D. Garcia-Dorado, H.M. Piper / Cardiovascular Research 69 (2006) 1–3

Myocardial reperfusion injury:
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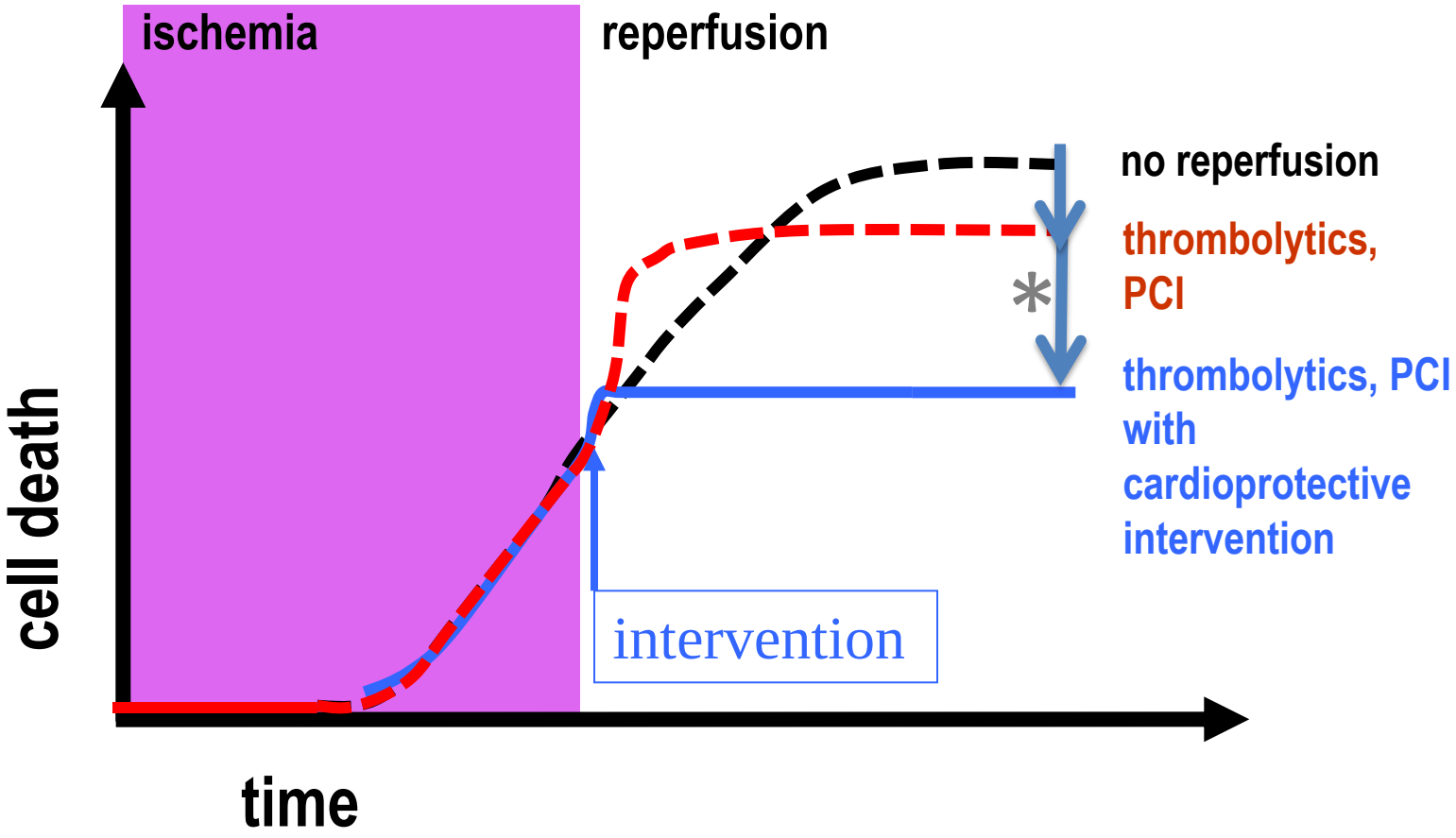


D. Garcia-Dorado, H.M. Piper / Cardiovascular Research 69 (2006) 1–3

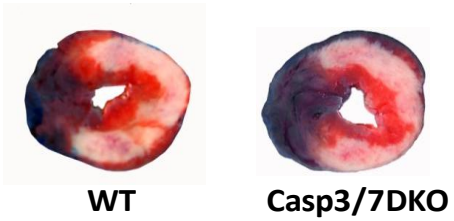
Mechanism of reperfusion injury in STEMI

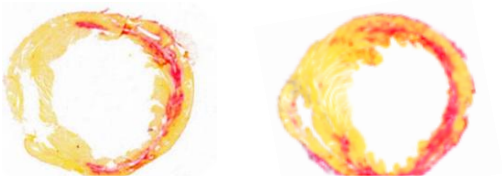
Mechanism of reperfusion injury in STEMI

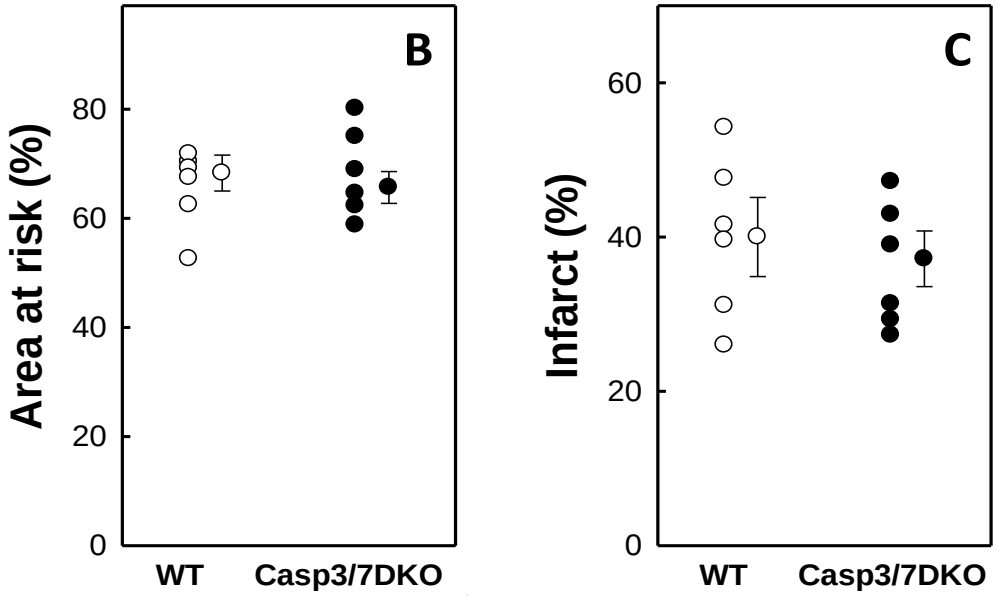
Nercrosis during the initial minutes of reflow

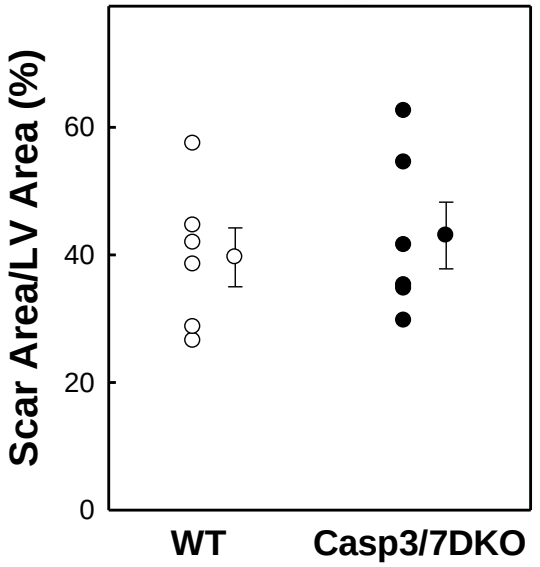
24 h reperfusion

28 days reoerfusion



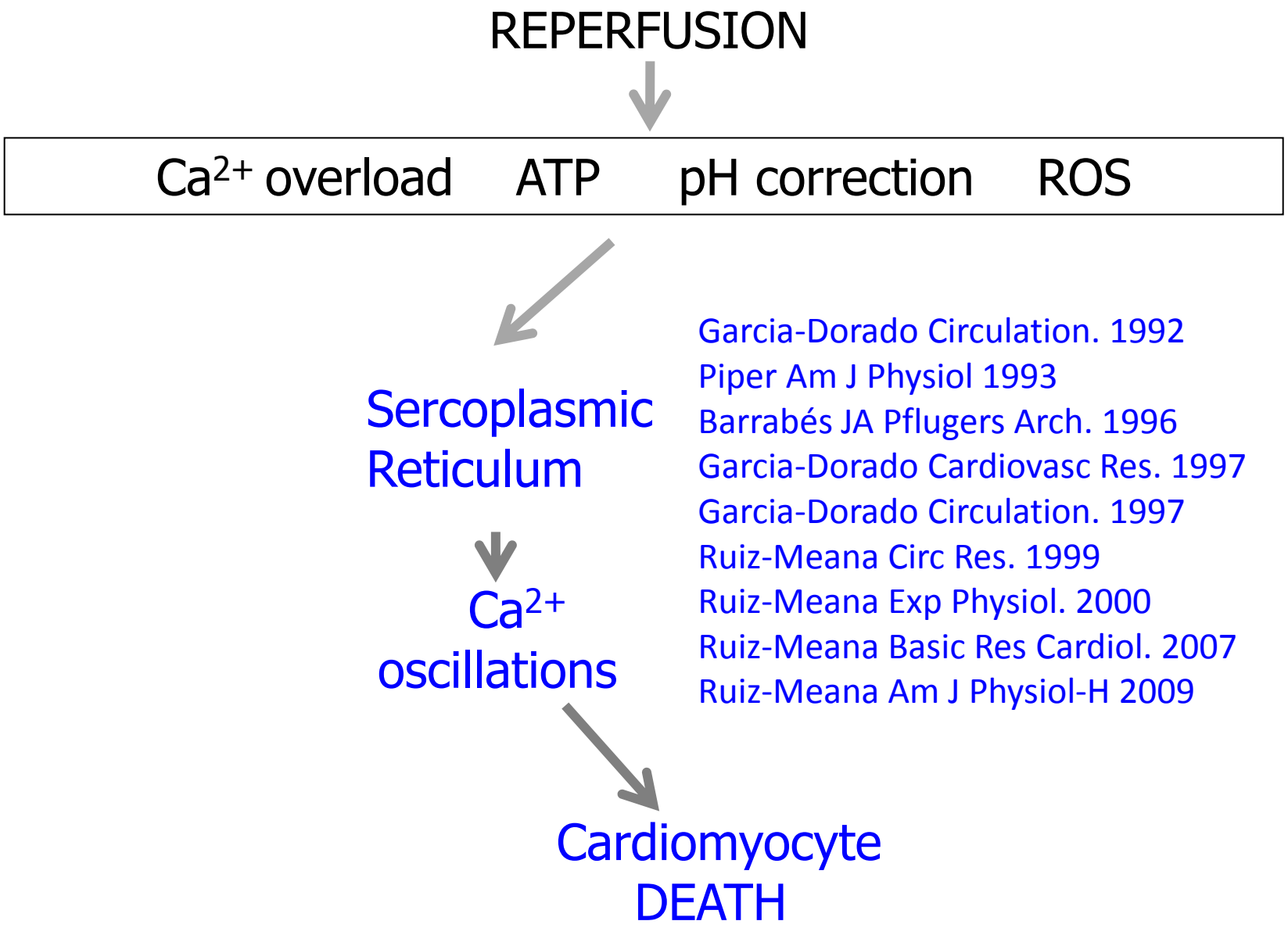




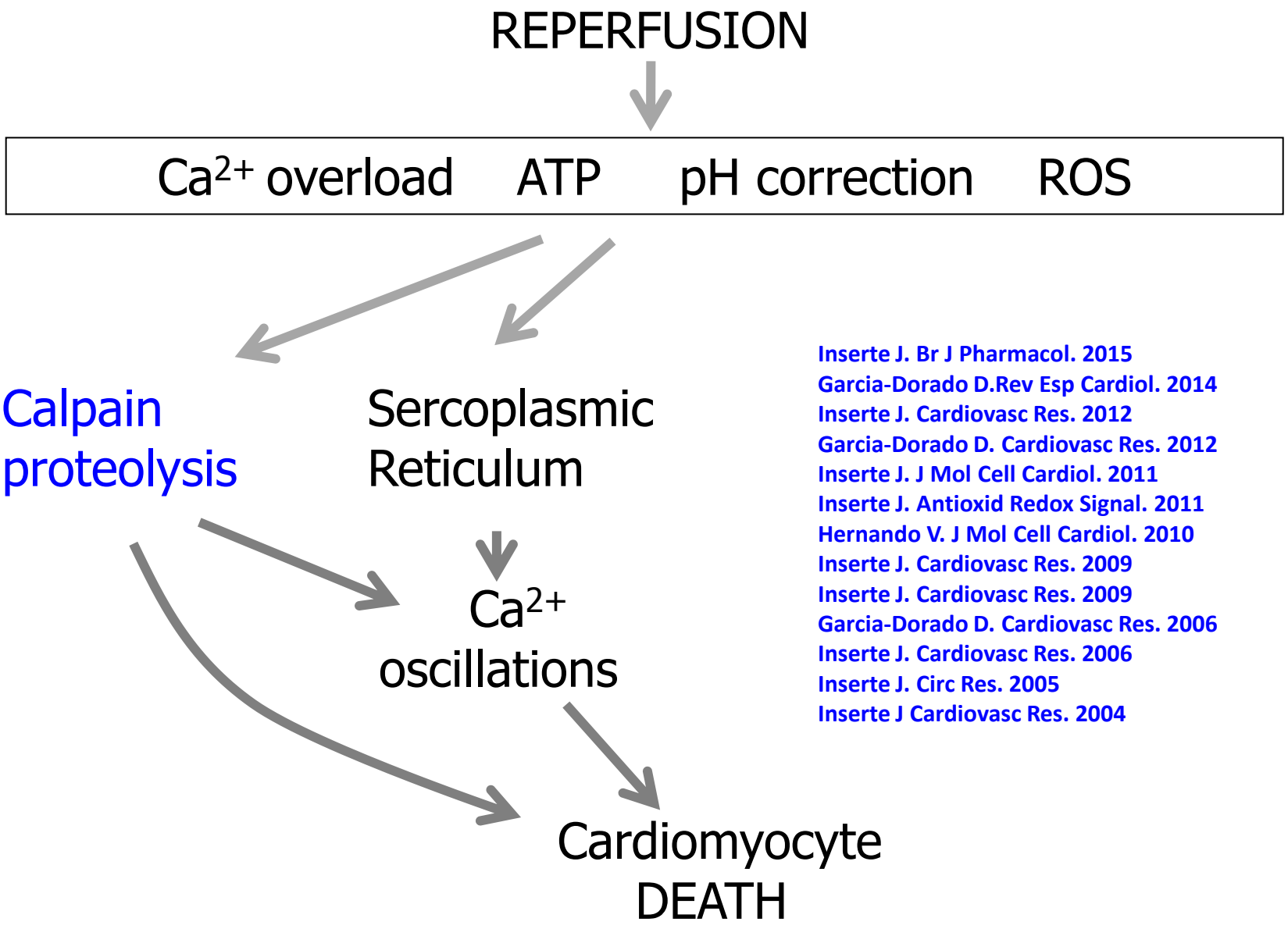


Inserte et al.. *Submitted*

Mechanism of reperfusion injury in STEMI

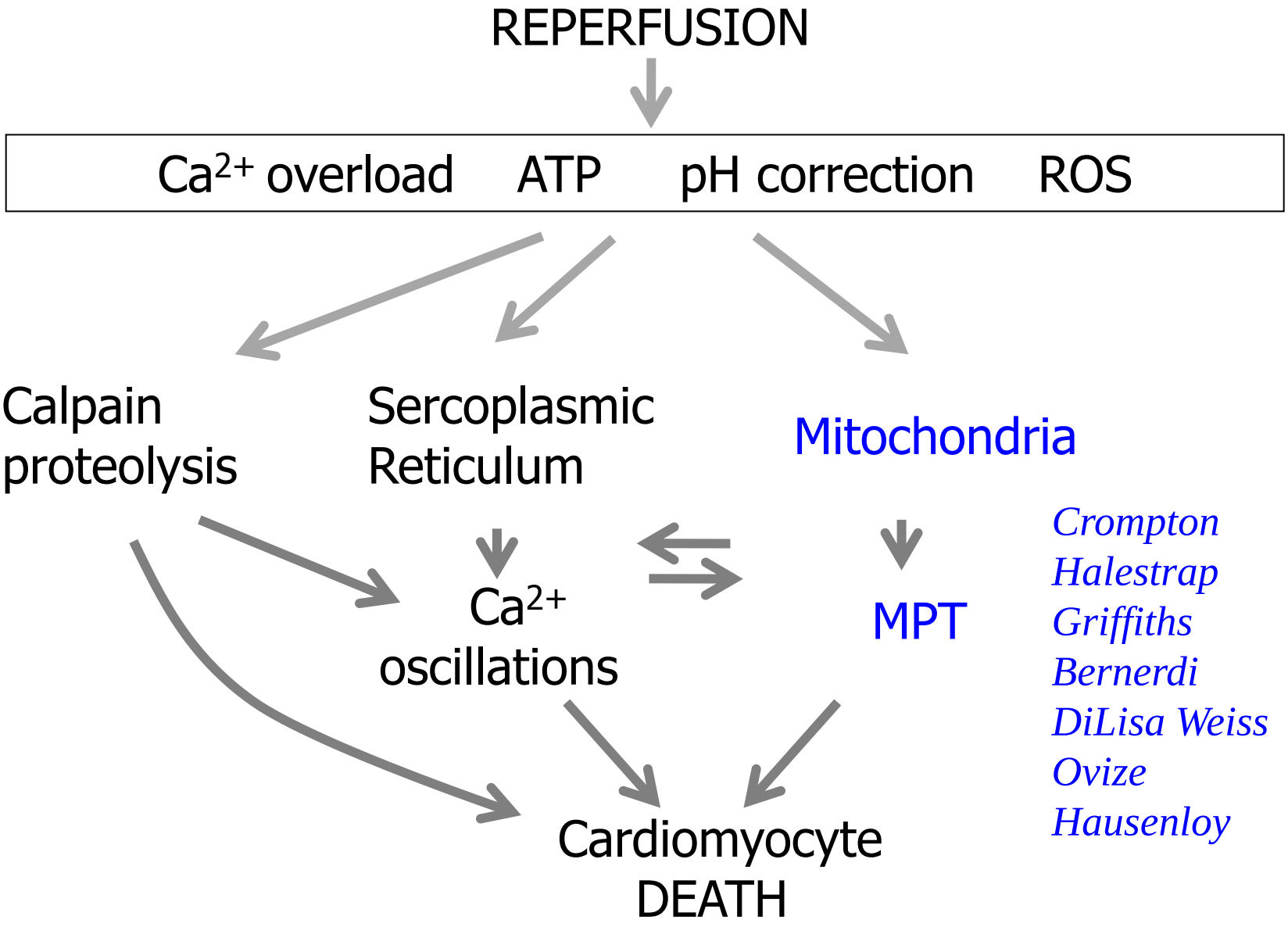


Mechanism of reperfusion injury in STEMI

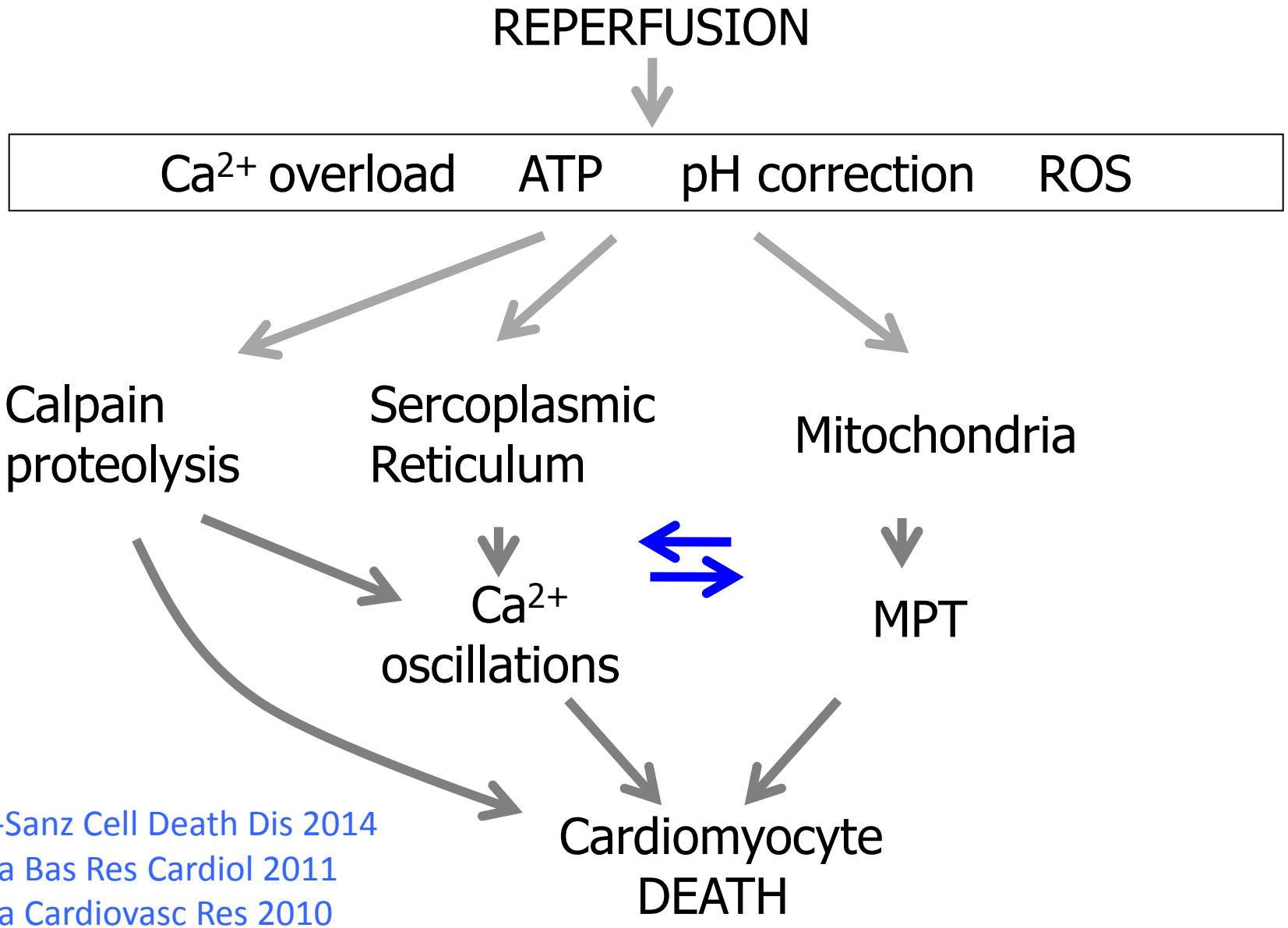


Inserte J. Br J Pharmacol. 2015
Garcia-Dorado D.Rev Esp Cardiol. 2014
Inserte J. Cardiovasc Res. 2012
Garcia-Dorado D. Cardiovasc Res. 2012
Inserte J. J Mol Cell Cardiol. 2011
Inserte J. Antioxid Redox Signal. 2011
Hernando V. J Mol Cell Cardiol. 2010
Inserte J. Cardiovasc Res. 2009
Inserte J. Cardiovasc Res. 2009
Garcia-Dorado D. Cardiovasc Res. 2006
Inserte J. Cardiovasc Res. 2006
Inserte J. Circ Res. 2005
Inserte J Cardiovasc Res. 2004

Mechanism of reperfusion injury in STEMI

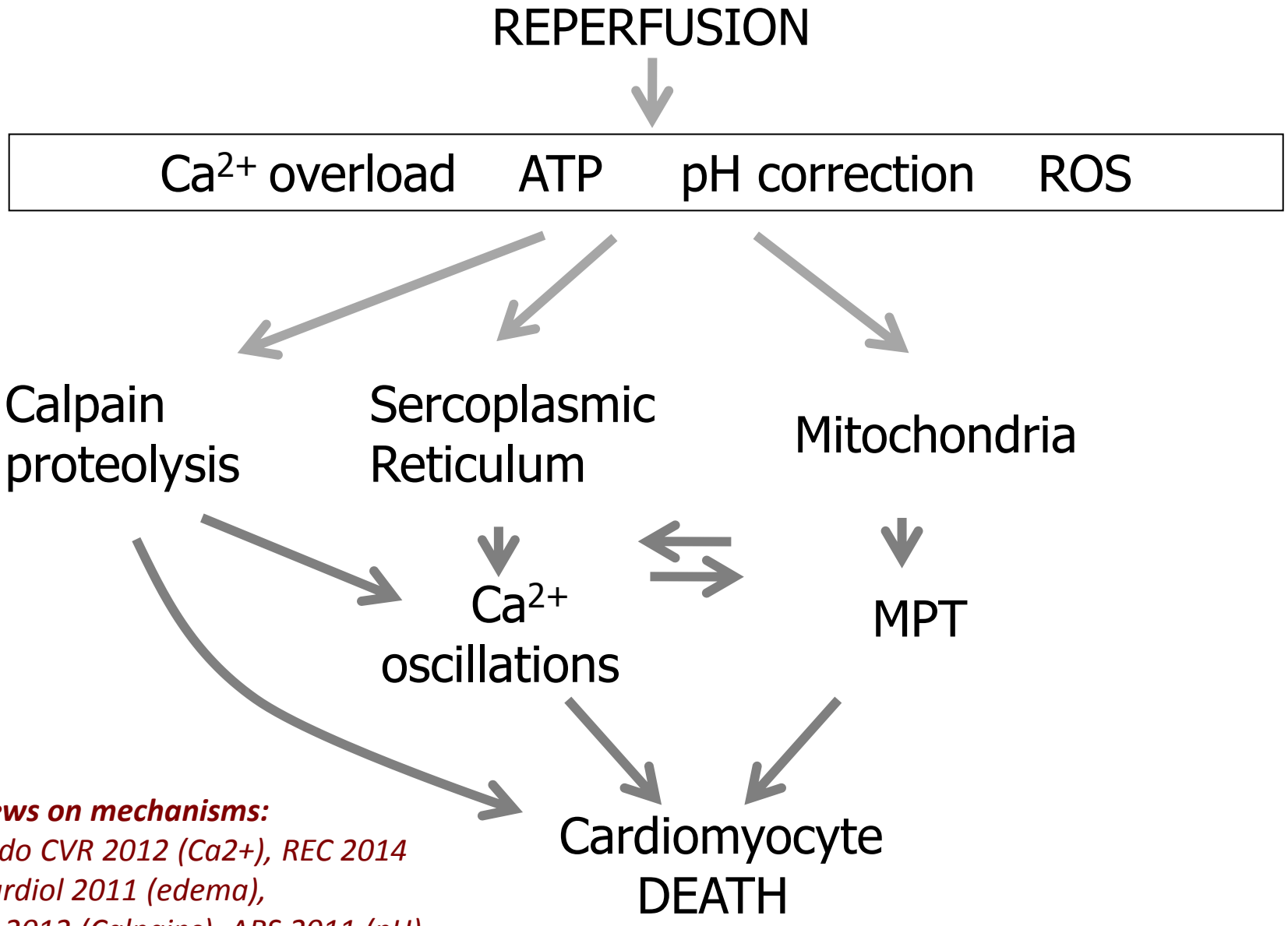


Mechanism of reperfusion injury in STEMI



Fernandez-Sanz Cell Death Dis 2014
Ruiz-Meana Bas Res Cardiol 2011
Ruiz-Meana Cardiovasc Res 2010
Ruiz-Meana Am J Physiol H 2009

Mechanism of reperfusion injury in STEMI



Recent reviews on mechanisms:

Garcia-Dorado CVR 2012 (Ca2+), REC 2014
J Mol Cell Cardiol 2011 (edema),
Inserte, CVR 2012 (Calpains), ARS 2011 (pH)
Rodriguez-Sinovas (Cx43), BBA 2012, Ruiz-Meana CVR 2011, BRC 2011(Mito-SR), Inserte (cGMP), BJP 2014

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Strategies to limit reperfusion injury in STEMI

Conditioning

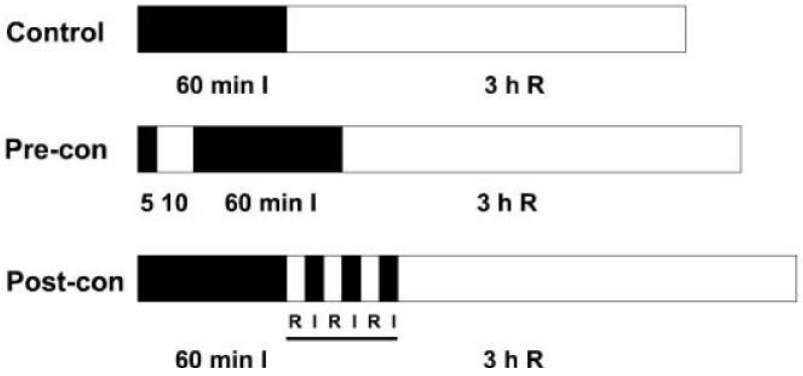
→ Ischemic post-conditioning

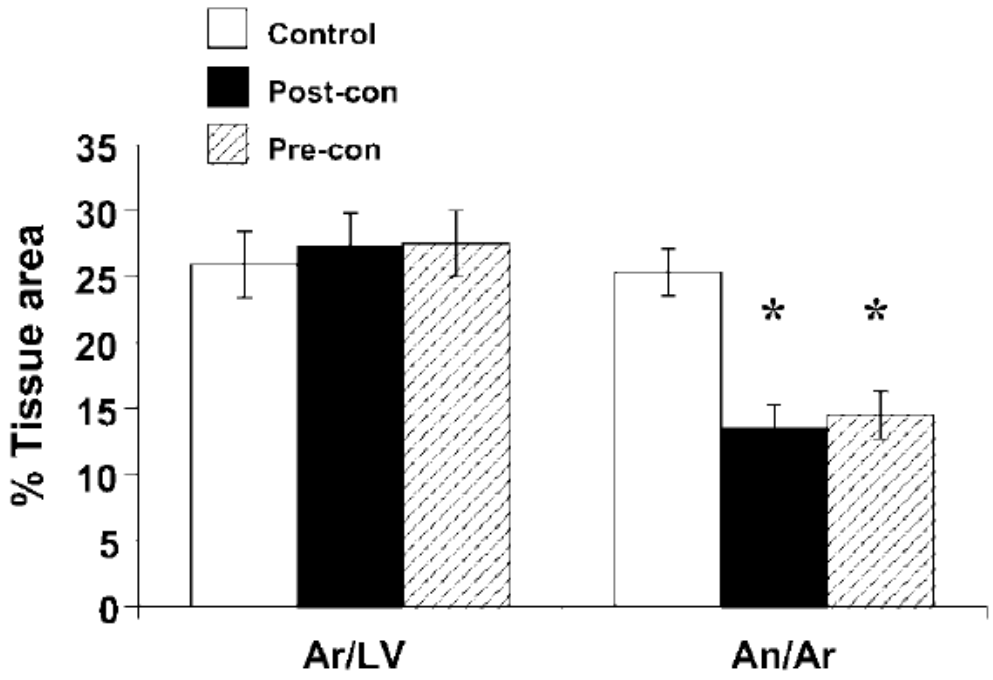
Remote ischemic conditioning

Other

Pharmacological treatments

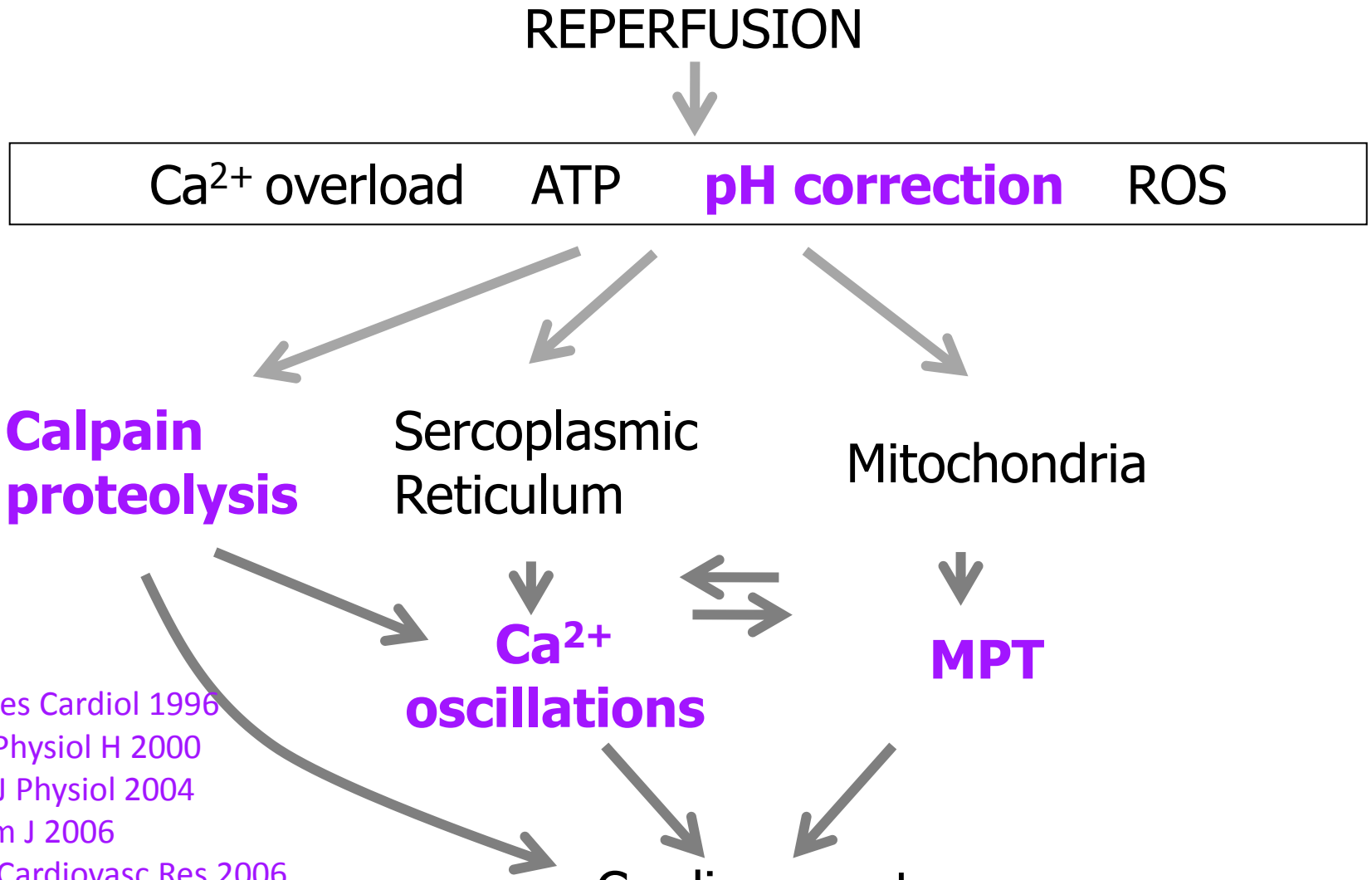
Ischemic postconditioning: brief periods of ischemia at the onset of reperfusion



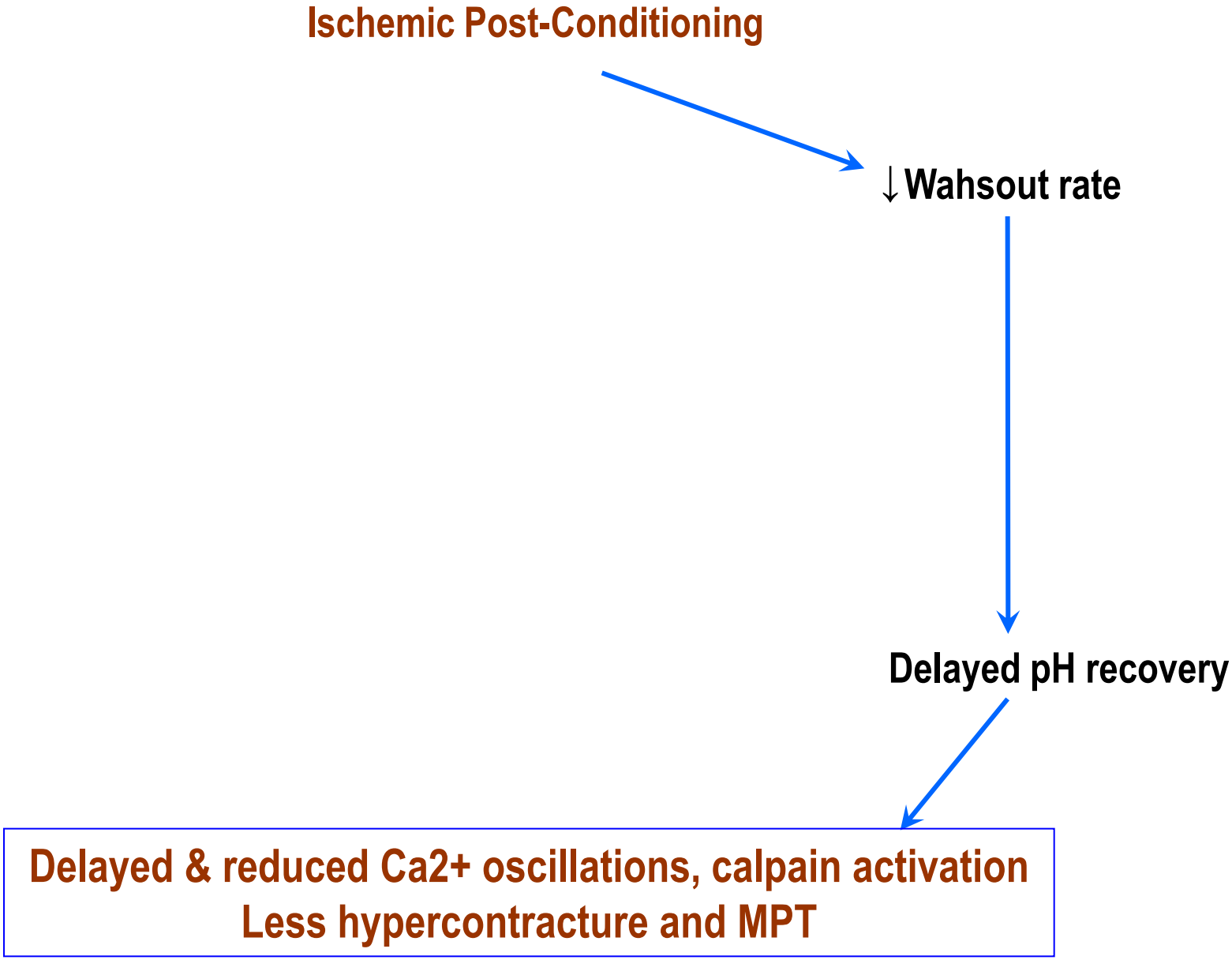


Zhao ZQ. Am J Physiol. 2003 Aug;285:H579-88

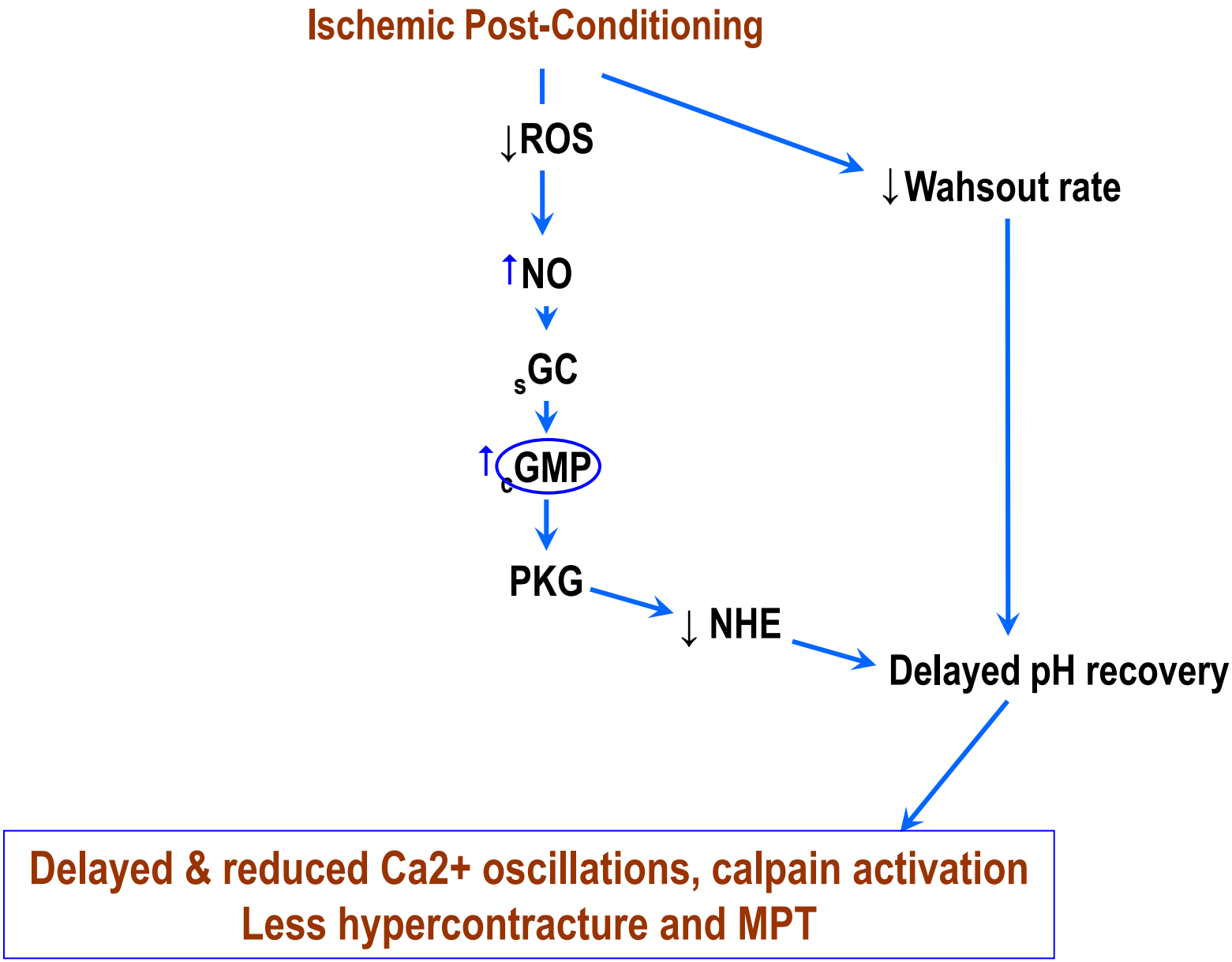
Mechanism of reperfusion injury in STEMI



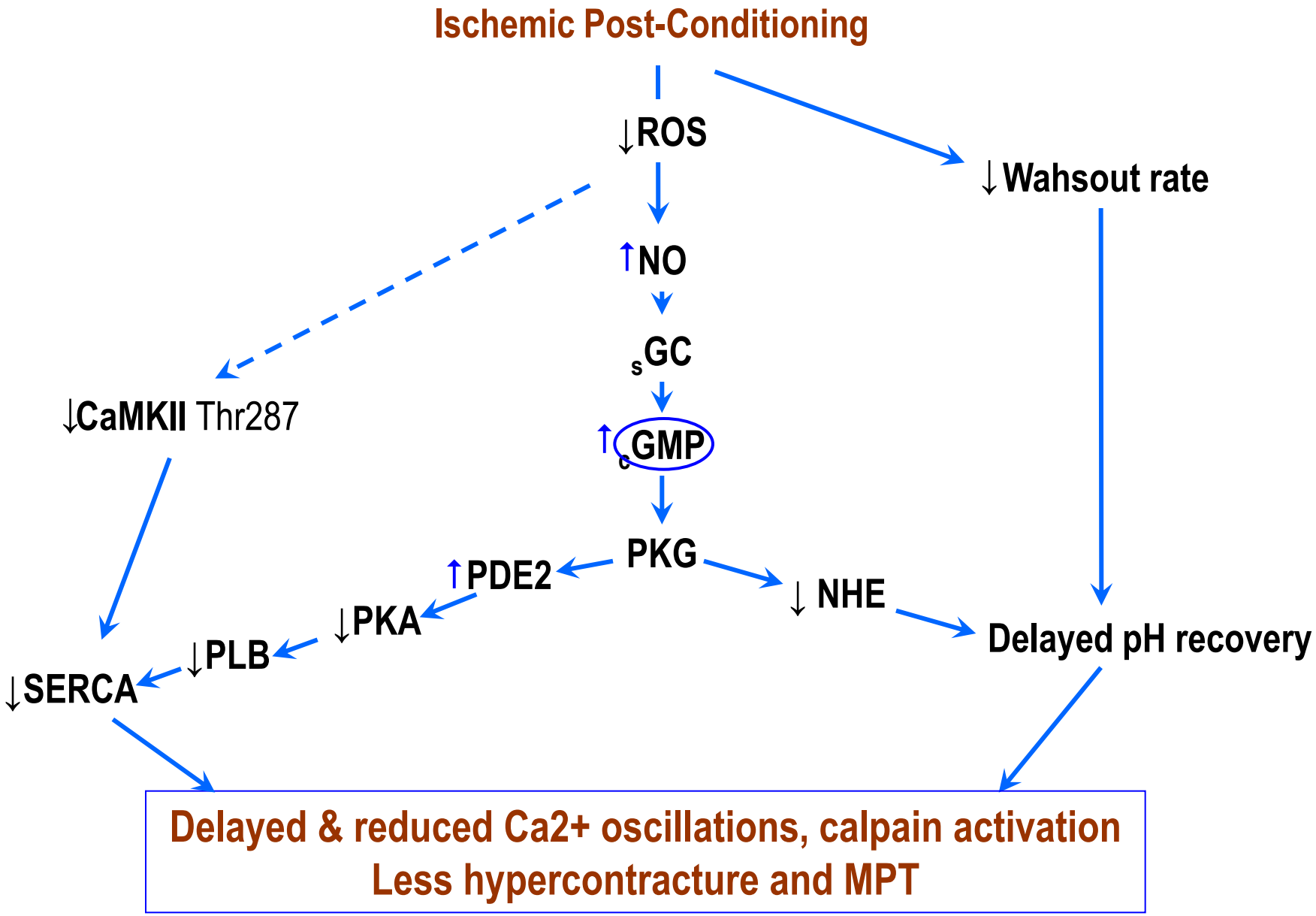
Piper Basic Res Cardiol 1996
Agulló Am J Physiol H 2000
Ruiz-Meana J Physiol 2004
Sarri Biochem J 2006
Ruiz-Meana Cardiovasc Res 2006
Inserte Cardiovasc Res 2008
Inserte Cardiovasc Res 2009
López Am J Physiol H 2008
Rodríguez-Sinovas A, Basic Res Cardiol 2009



Inserte et al. JMCC 2011, JAHA2013, CVR 2014



Inserte et al. JMCC 2011, JAHA2013, CVR 2014



Inserte et al. JMCC 2011, JAHA2013, CVR 2014

Effect of IPoCo on infarct size in patients with STEMI

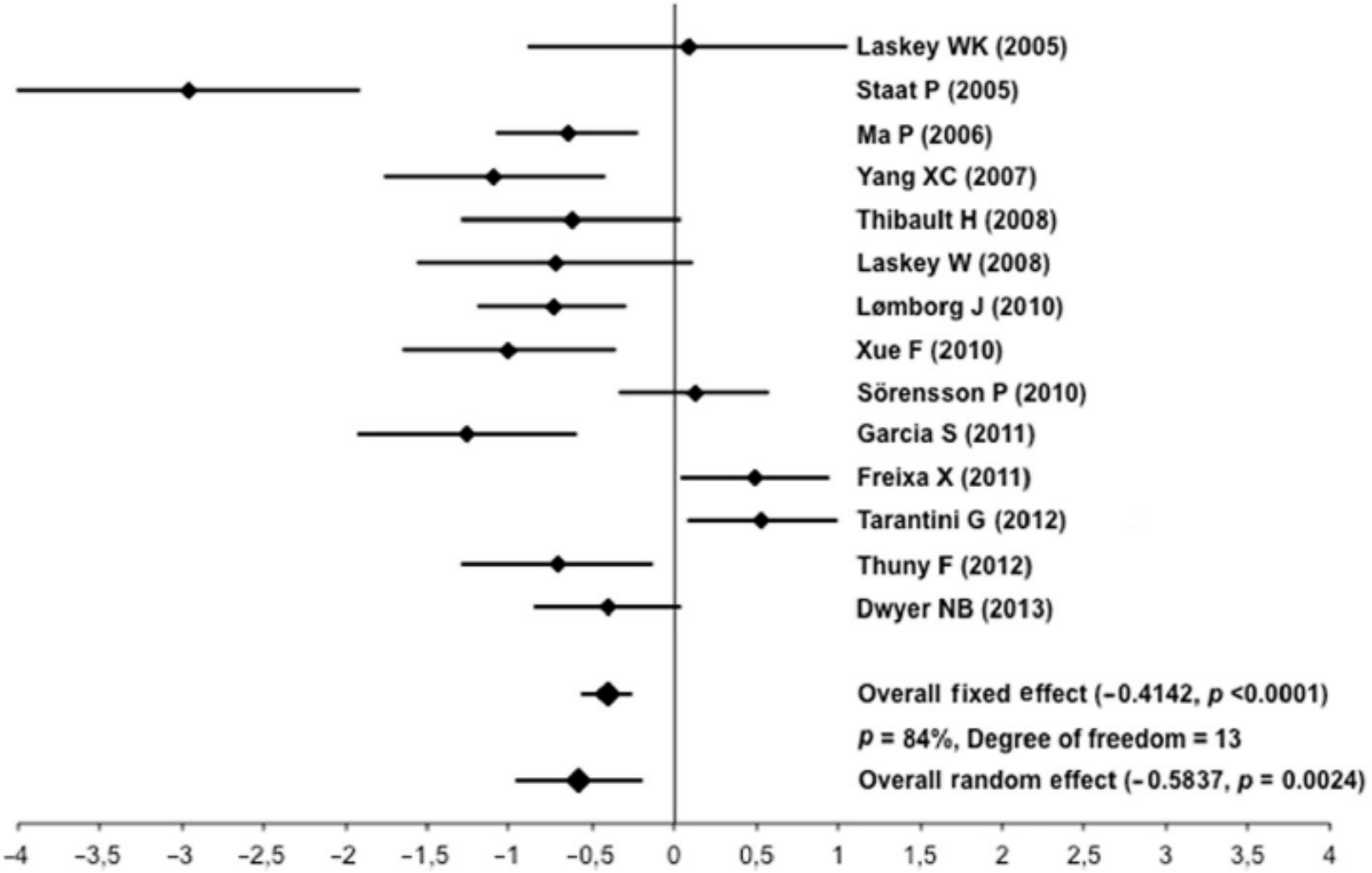


Figure 2. Forest plot for infarct size, expressed as weighted standardized mean difference.

Favaretto: Am J Cardiol 2014;114:946e 952

Strategies to limit reperfusion injury in STEMI

Conditioning

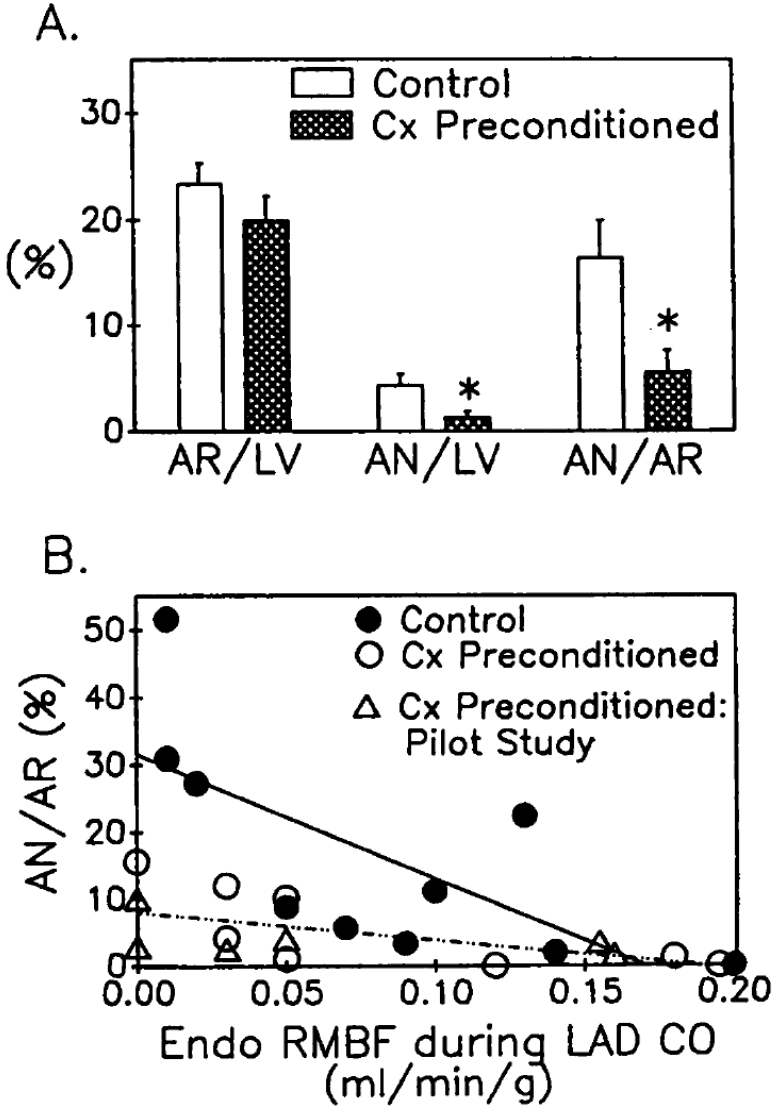
- Ischemic post-conditioning
- → Remote ischemic conditioning
- Other

Pharmacological treatments

Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion

K Przyklenk, B Bauer, M Ovize, RA Kloner and P Whittaker

Circulation 1993, 87:893-899

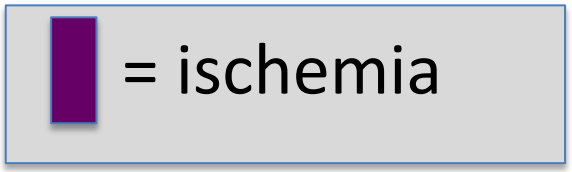


FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC)

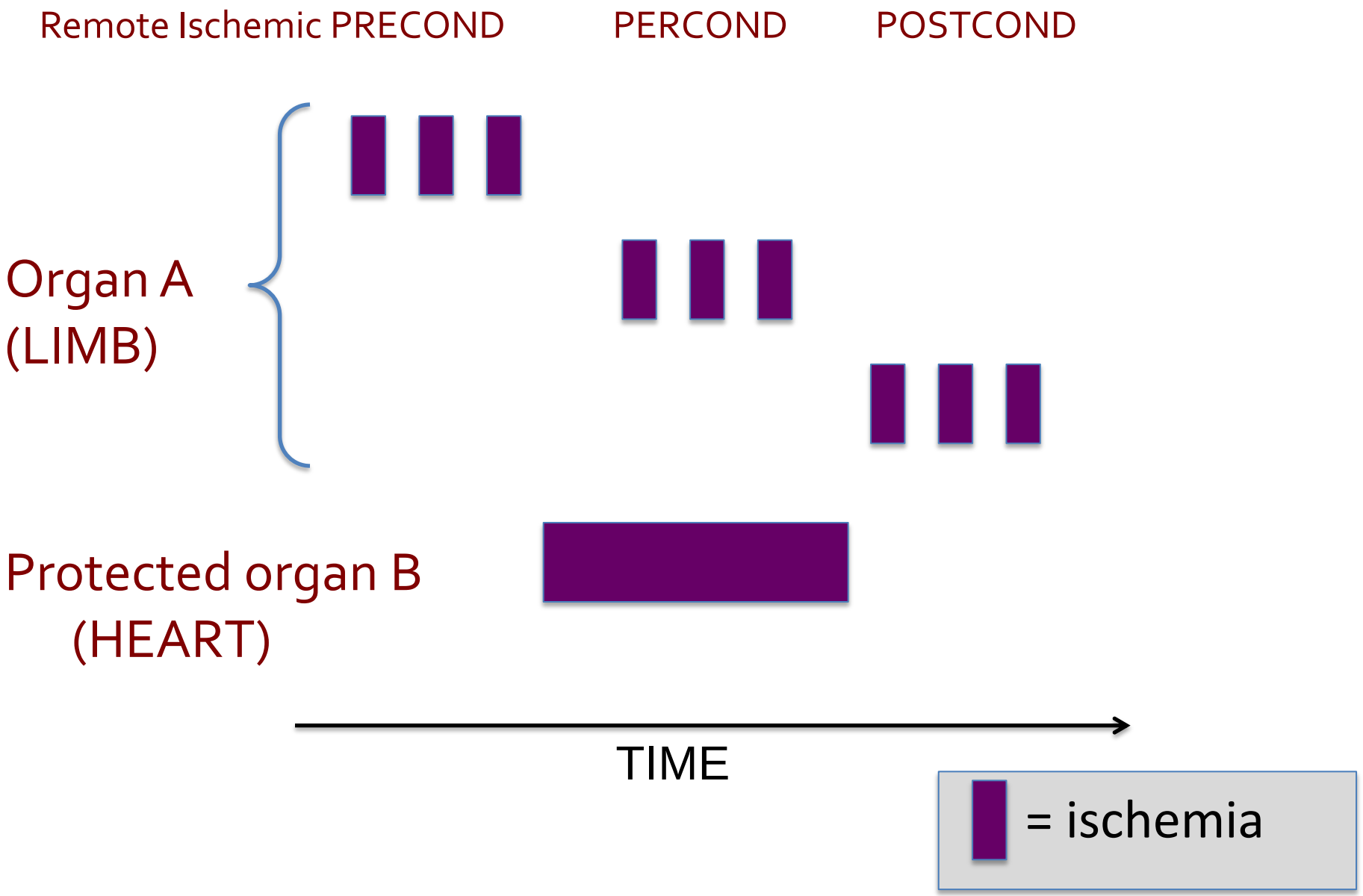
Remote Ischemic PRECOND PERCOND POSTCOND

Protected organ B
(HEART)

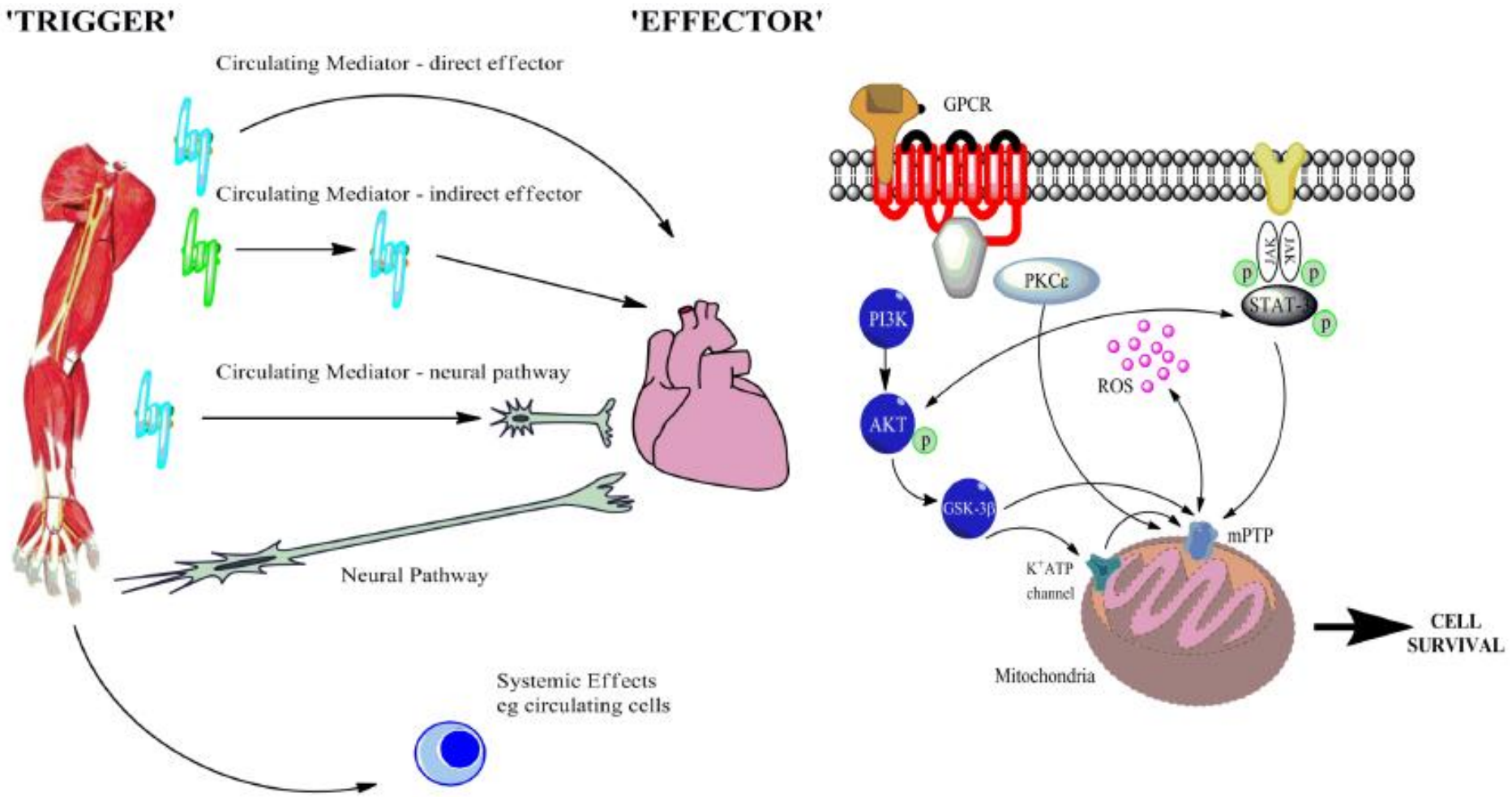
TIME



FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC)

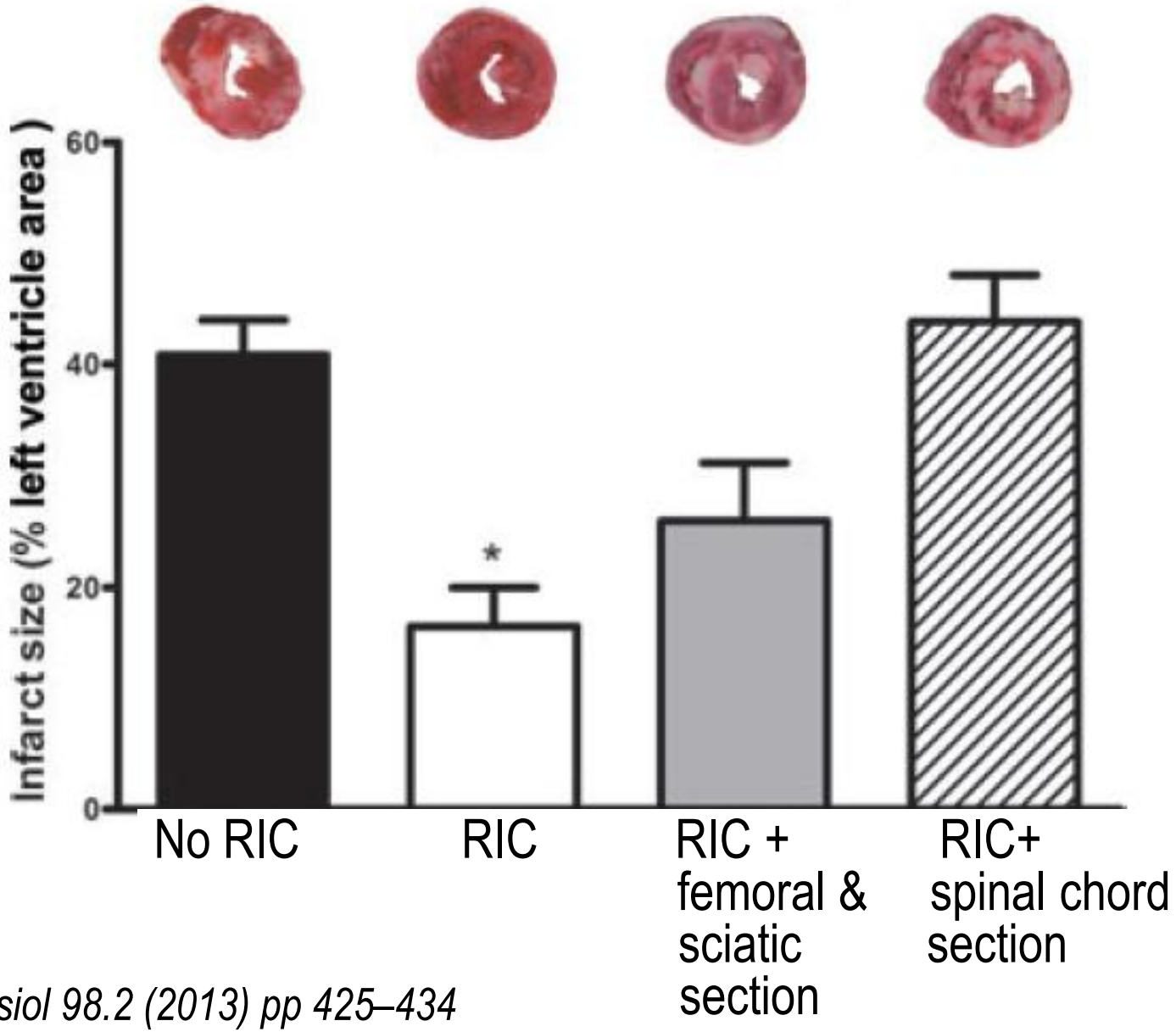


Triggers, mediators and effectors of RIC



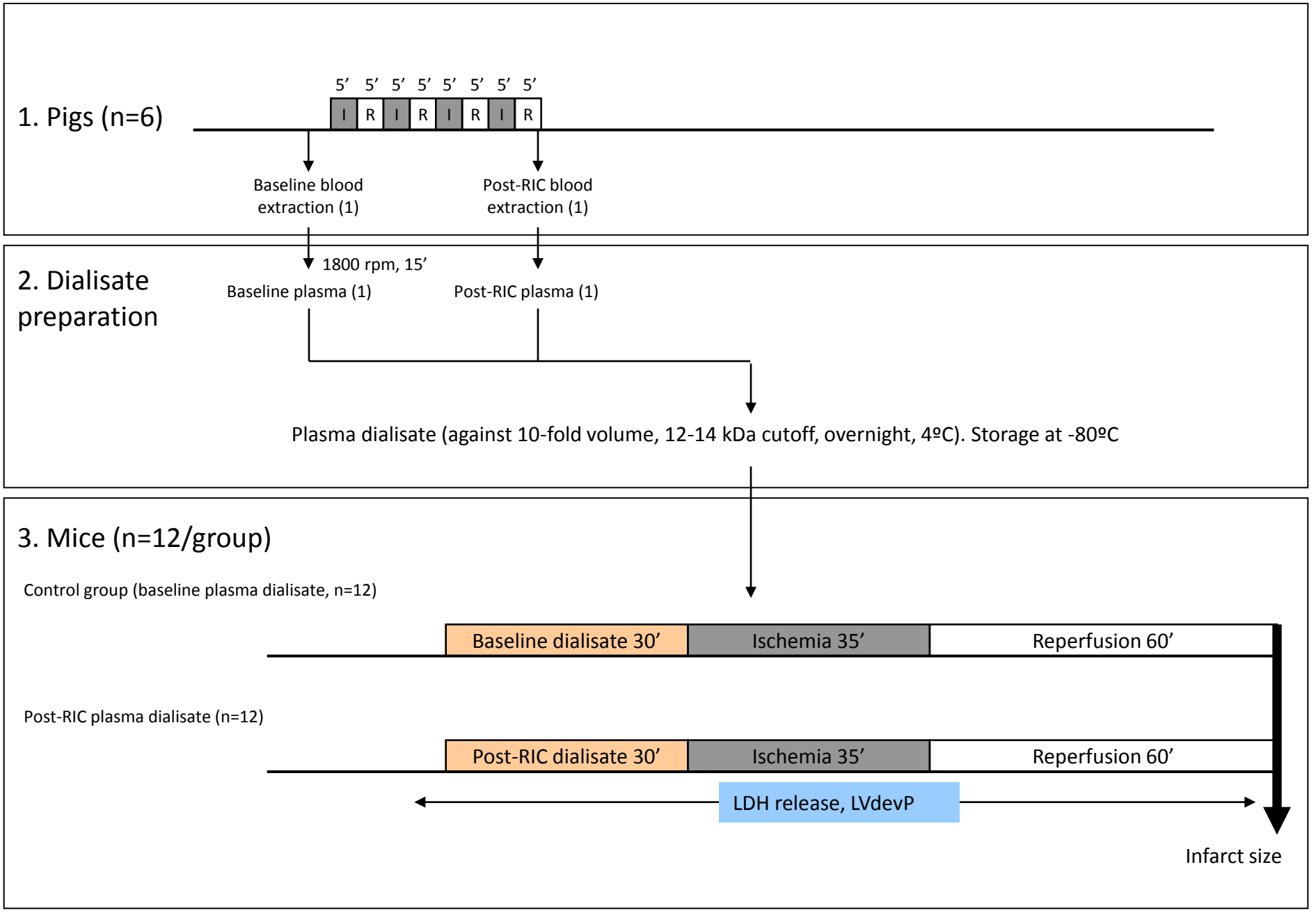
Rajesh K Kharbanda: ESC 2012

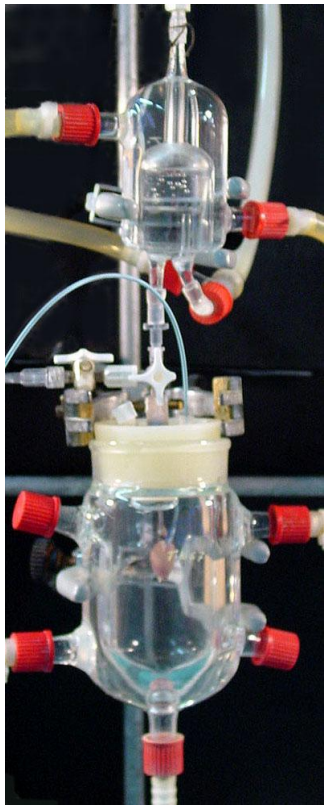
Rople of parasympathic nerve in RIC (femoral occlusions) induced cardioprotection in isolated rabbit hearts



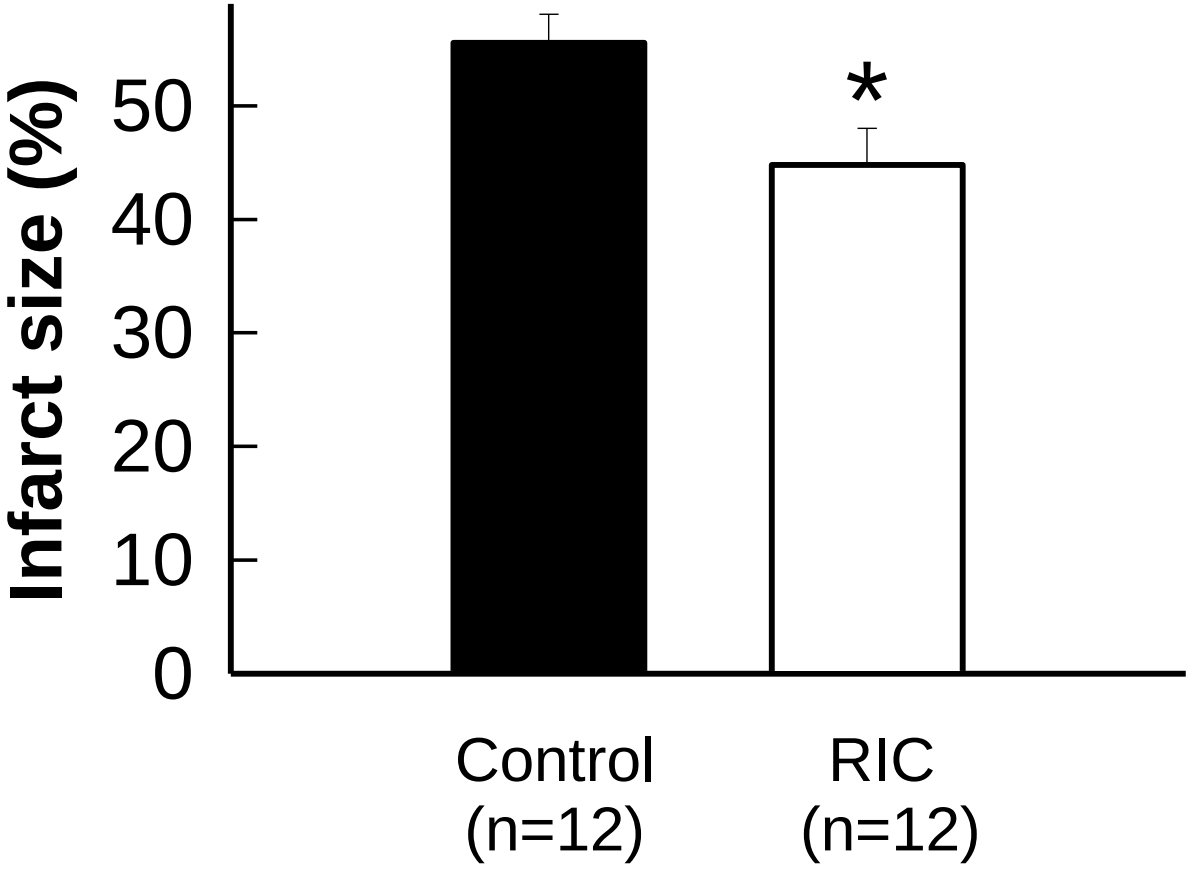
Donato et al . Exp Physiol 98.2 (2013) pp 425–434

PLASMA FROM RIC PIGS PROTECTS ISOLATED MICE HEARTS



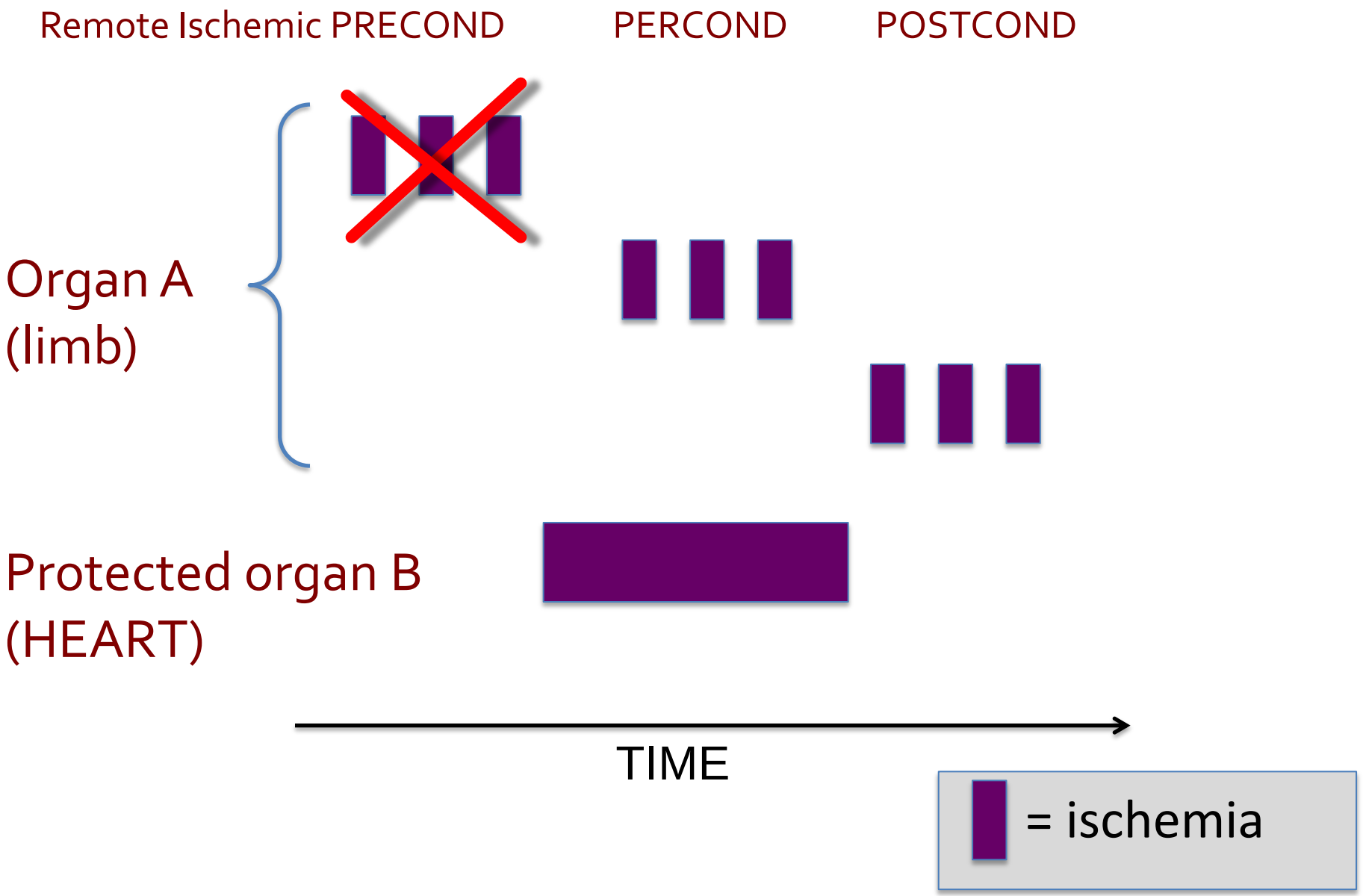


PLASMA FROM RIC PIGS PROTECTS ISOLATED MICE HEARTS

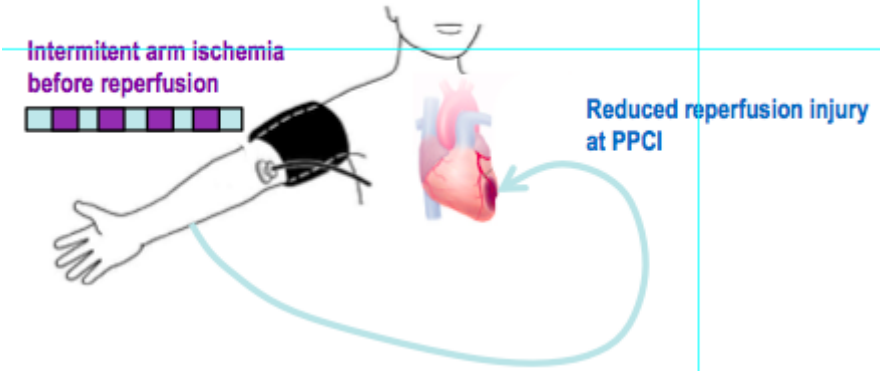


Alburqueque-Bejar et al. *Unpublished*

FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC) **IN STEMI PATIENTS**



Remote Ischemic conditioning in STEMI: clinical trials



Study	N number (Control vs. RIC)	Clinical setting	RIC protocol (site of delivery)	Endpoint	Infarct size
Rentoukas *et al.*[44]	30 vs. 33	STEMI (pPCI) with morphine	4 x 5 min arm I/R (Hospital)	Troponin I peak	↓ (40%)
CONDI-1 Botker *et al.*[26]	69 vs. 73	STEMI (pPCI)	4 x 5 min arm I/R (Ambulance)	SPECT myocardial salvage index	↓(36%)
Munk *et al.*[56]	33 vs. 31	Anterior STEMI(pPCI)	4 x 5 min arm I/R (Ambulance)	SPECT MI size(30 days)	↓ (56%)
RIPOST-MI Prunier *et al.*[67]	17 vs. 18	STEMI (pPCI)	3 x 5 min arm I/R (Hospital)	AUC CK-MB/AAR	↓ (33%)
Crimi *et al.*[46]	48 vs. 48	Anterior STEMI (pPCI)	4 x 5 min leg I/R (Hospital)	AUC CK-MB	↓ (20%)
ERIC-STEMI White et al[68]	43 vs. 40	STEMI (pPCI)	4 x 5 min arm I/R (Hospital)	MI size (MRI)	↓ (27%)
ERIC-LYSIS Hausenloy et al[69]	206 vs. 208	STEMI (Thrombolysis)	4 x 5 min arm I/R (Hospital)	AUC CK-MB AUC Trop T	↓ (18%) ↓ (16%)

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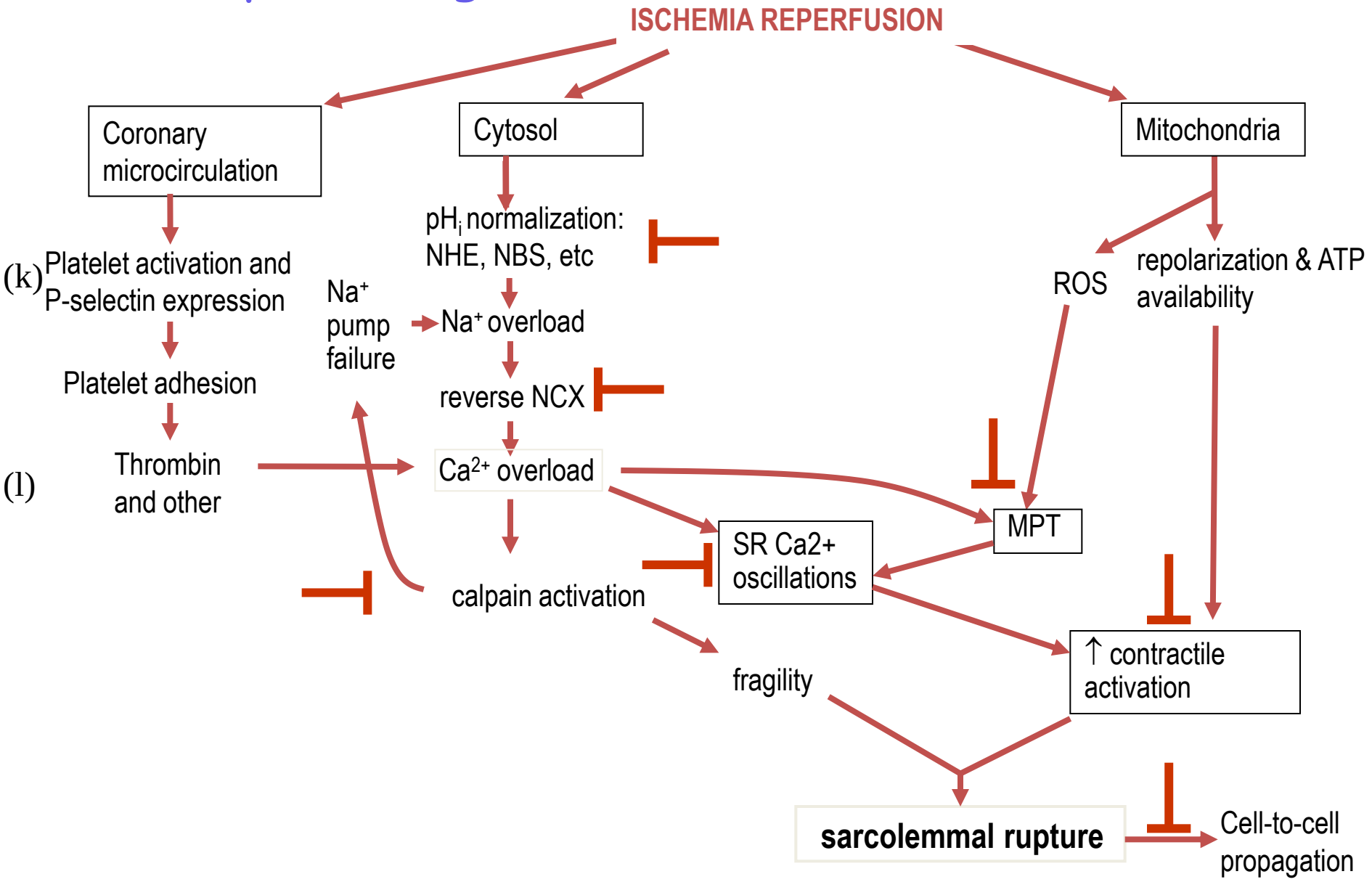
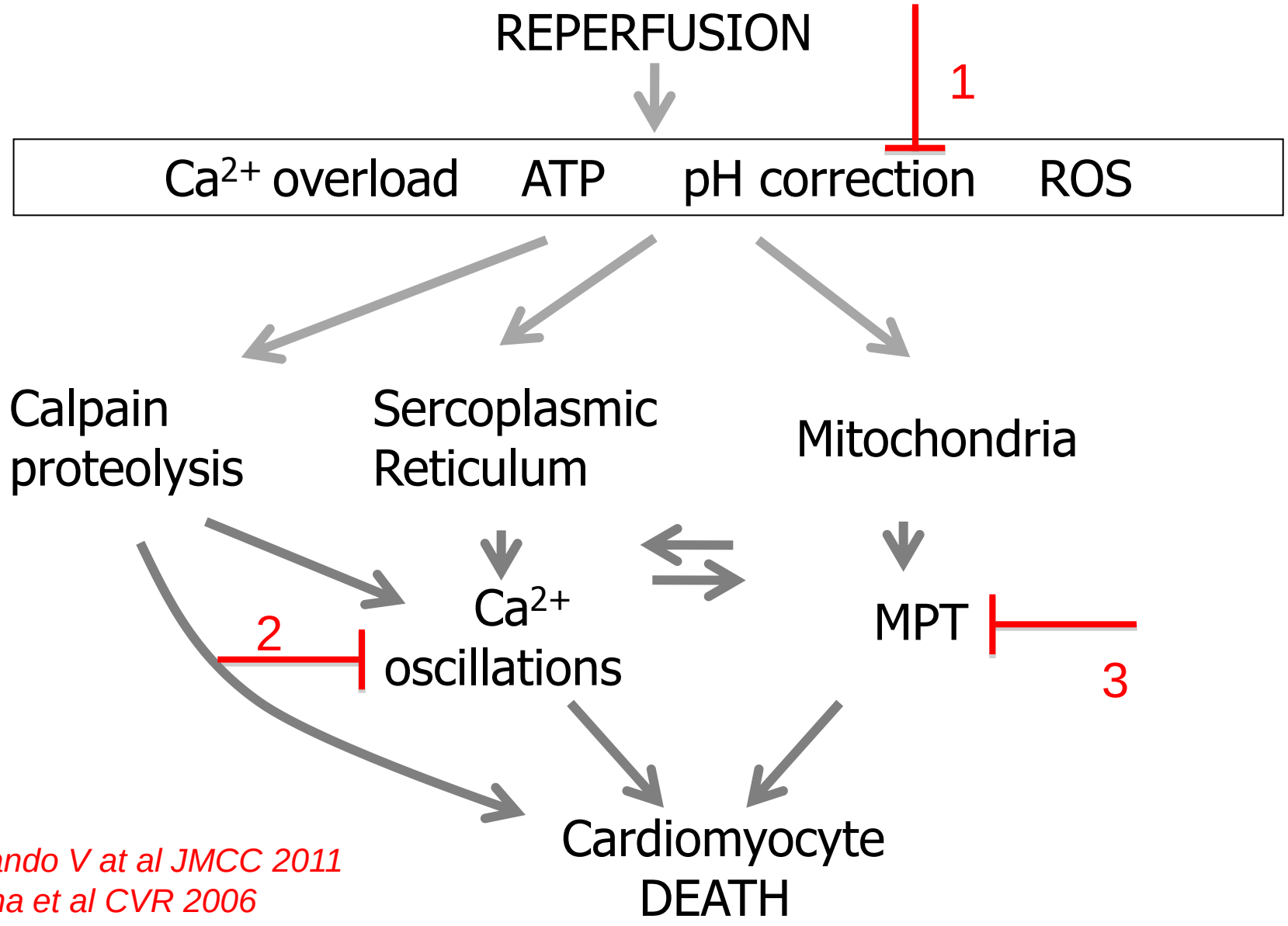
Reperfusion injury in STEMI: unsolved issues and limitations

Orphan targets

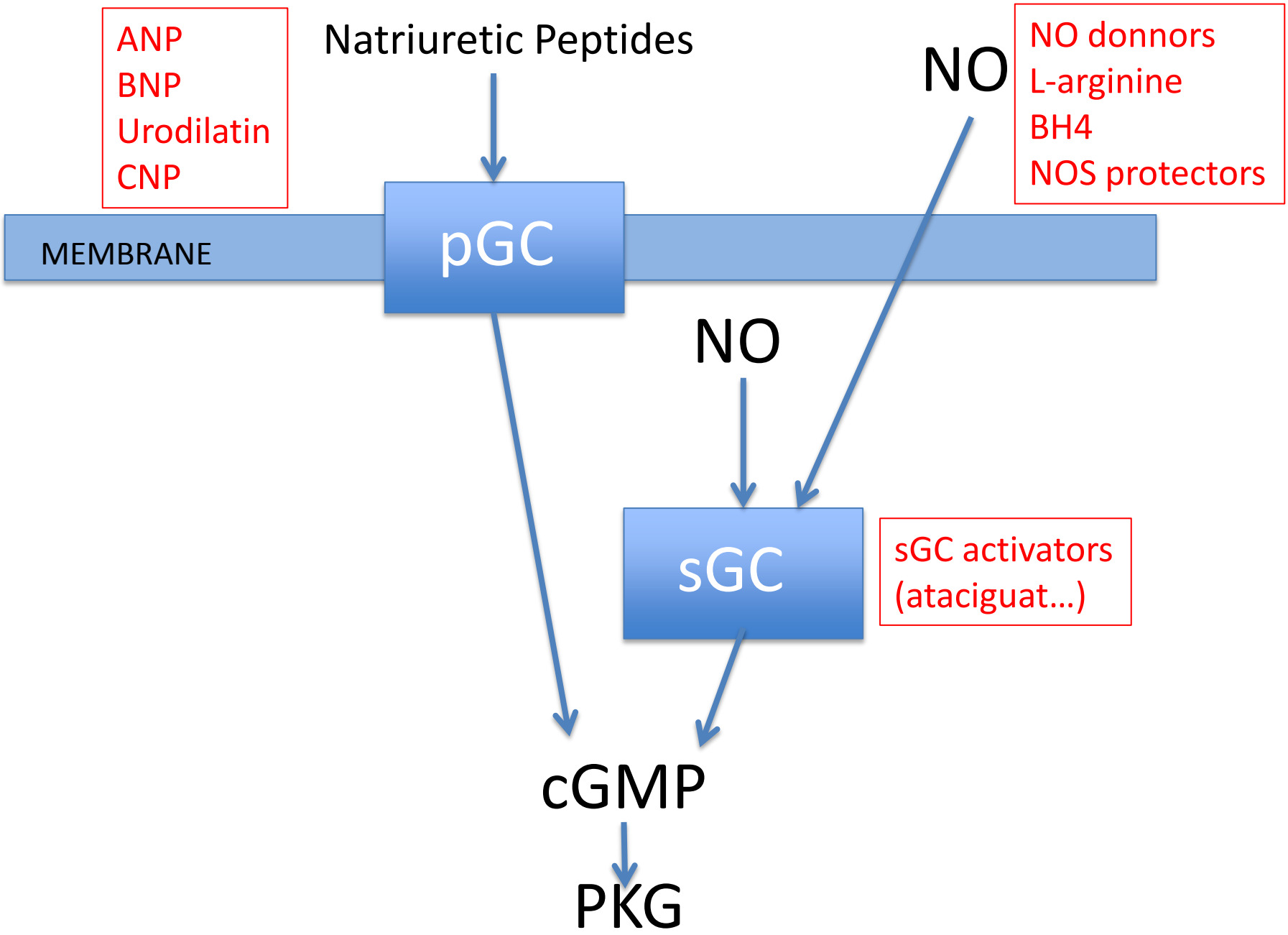


PKG signaling is cardioprotective

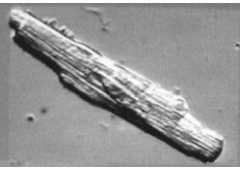


1. *Hernnando V at al JMCC 2011*
2. *Abdallha et al CVR 2006*
3. *Penna C, J Mol Cell Med 2008*

Pharmacological increase of myocardial cGMP-PKG signaling in STEMI



Pharmacological protection against reperfusion injury: PKG



Stimulation of cGMP synthesis with ANP prevents reoxygenation-induced hypercontracture

Hempel et al. Am J Physiol 1997;273: H244-9

Hypoxia and acidosis impair cGMP syntesis in coronary endothelium and cardiomyocytes

Agulló L, Am J Physiol 2002;283(:H917-25 and Am J Physiol 2003:284(6):H2170-6.

L-arginine limits reperfusion injury by a cGMP-dependent mechanism

Agulló L, Am J Physiol. 1999 ;276(:H1574-80.

Urodilatine at reperfusion limmits necrosis in rat hearts

Inserte et al, Cardiovasc Res 2000; 45:351-9.

Pretreatment with intravenous of L- arginine limmits infarct size in pigs

Pdilla F, Cardiovasc Res. 2000;46: 412-20.

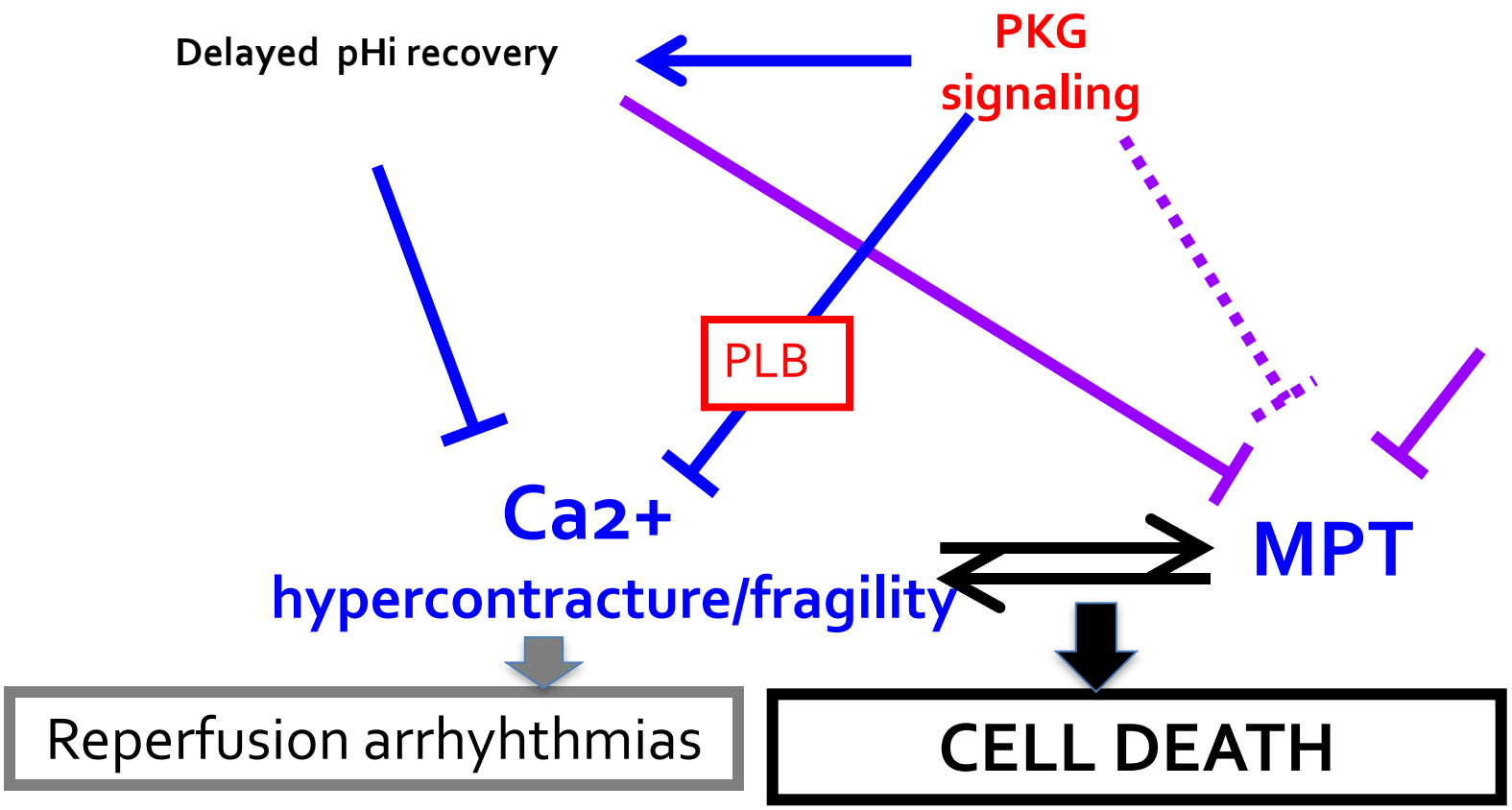
I.v. urodilatin at the time of coronary reperfusion limmits infarct size

Padilla et al, Cardiovasc Res 2001;15:592-600.

I.v. ataciguat reduces infarct size secondary to transient LAD occlusion in rats

Inserte et al. Cardiovasc Res. 2014;103:542-53

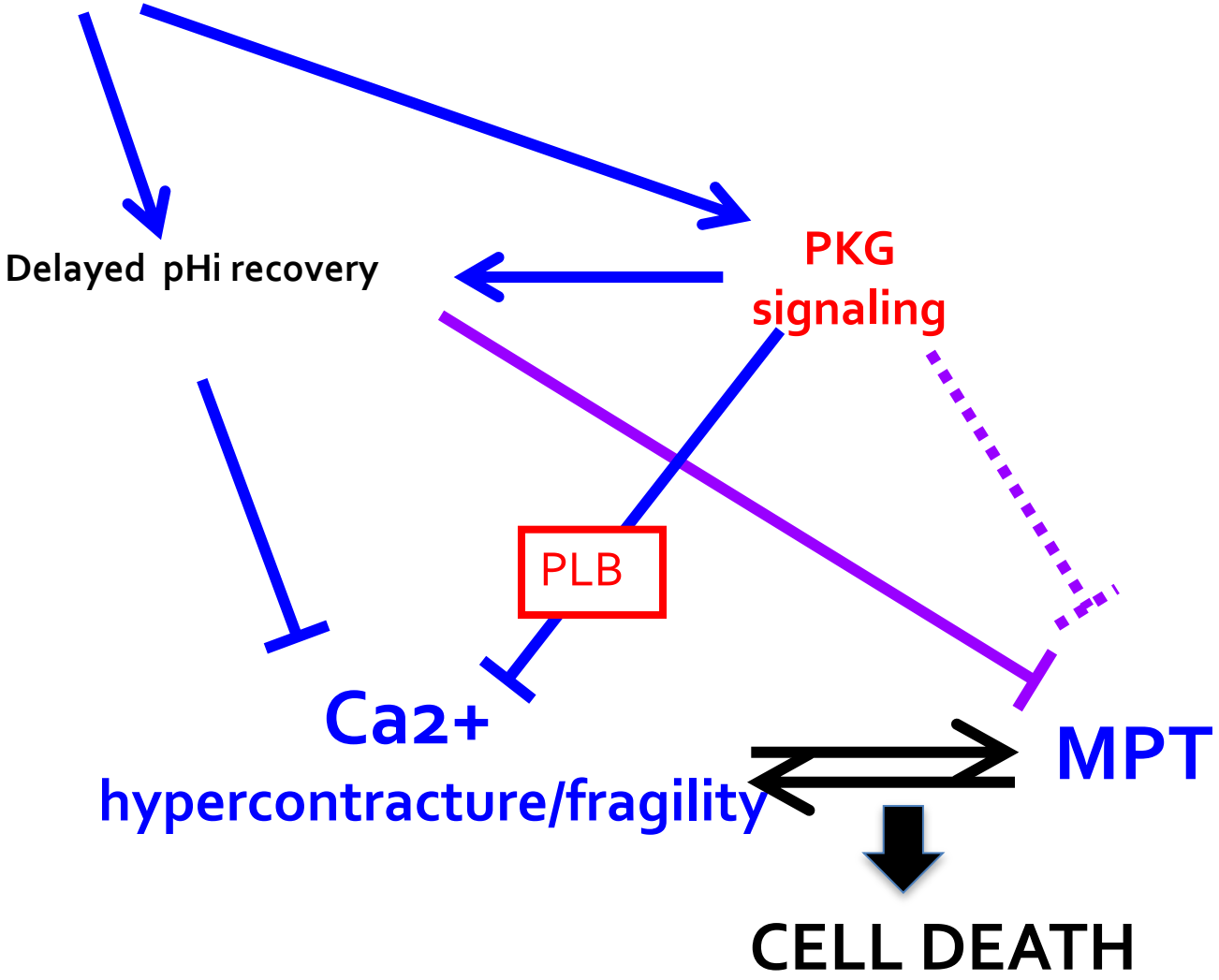
Clinical trials potentially involving PKG activation



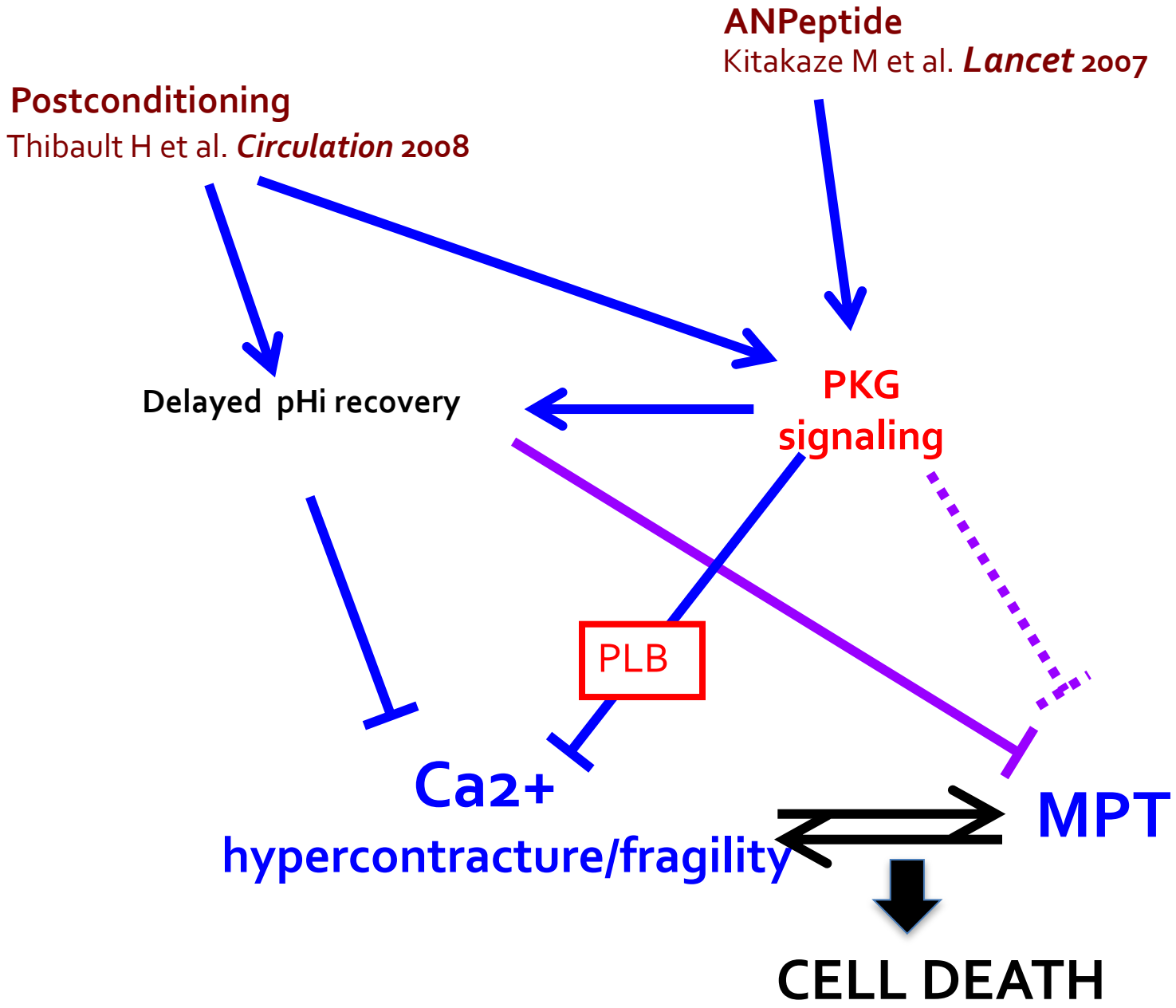
Clinical trials potentially involving PKG activation

Postconditioning

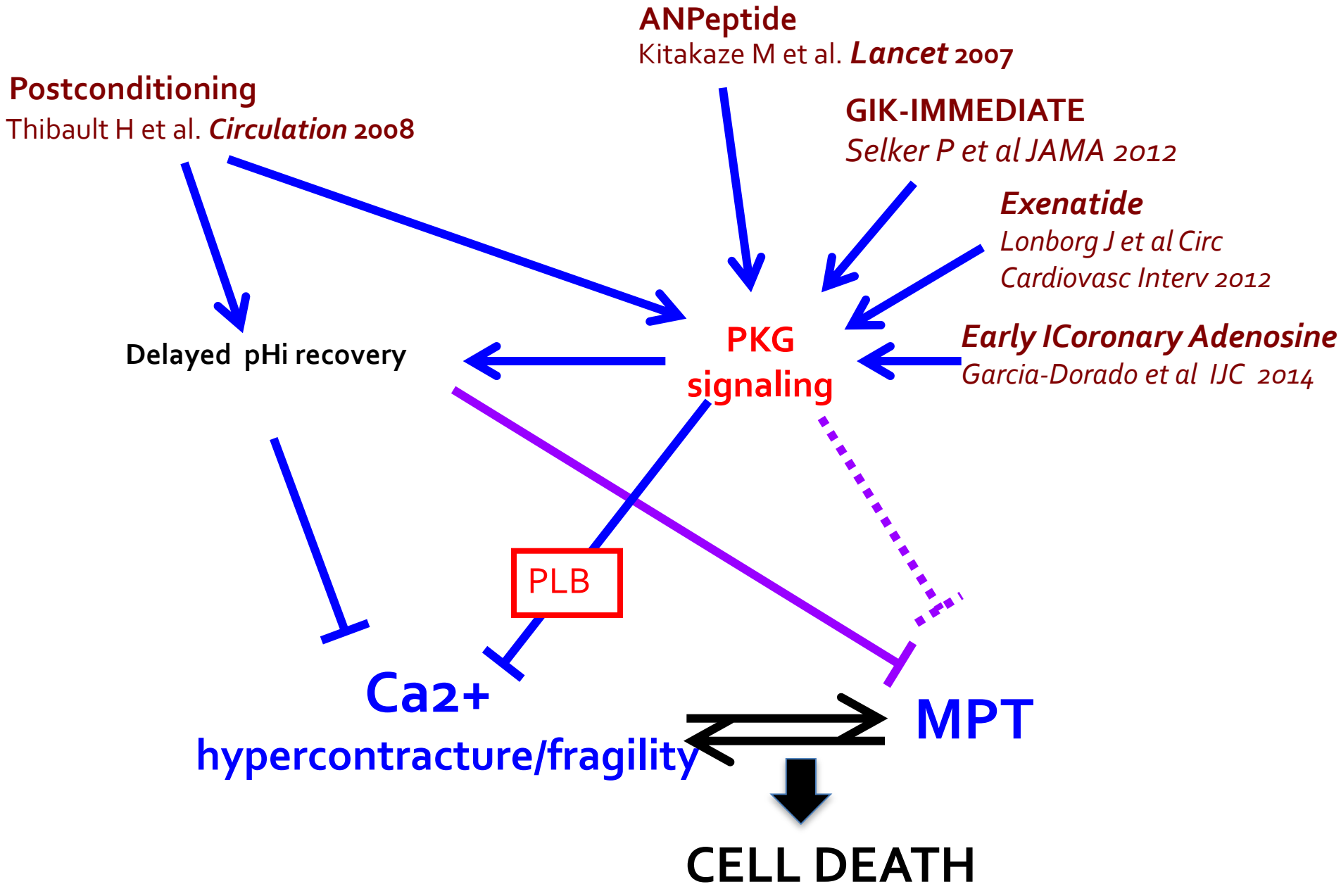
Thibault H et al. ***Circulation*** **2008**



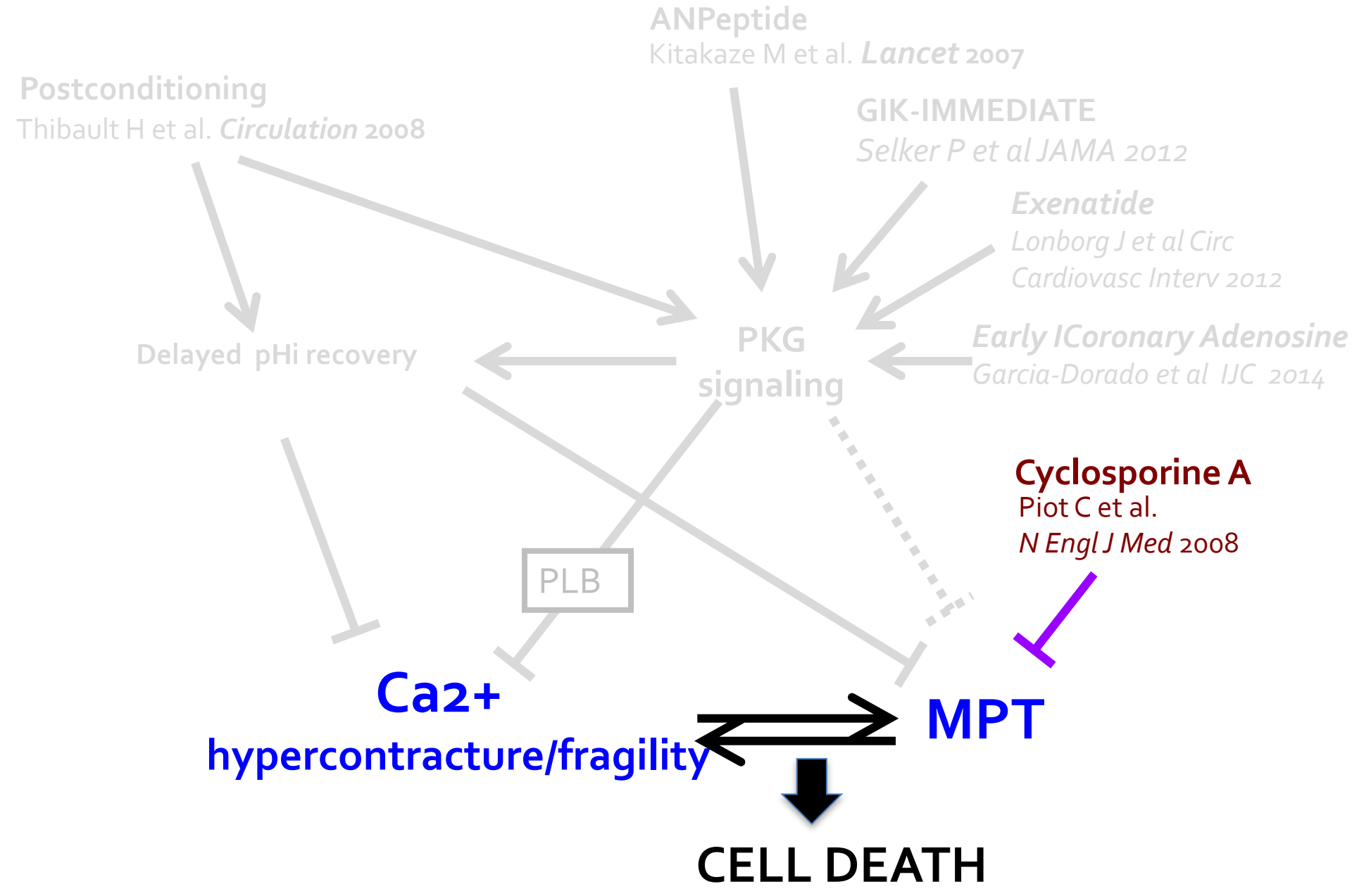
Clinical trials potentially involving PKG activation



Clinical trials potentially involving PKG activation



Clinical trials aiming at MPT: Direct MPT inhibition



Cardioprotective Therapy	Independent Clinical Trials – Number of Patients	Therapeutic intervention	Clinical Outcome	General Observations
Atrial Natriuretic Peptide	J-WIND-ANP* (N=569)	IV capertide 72h infusion started after reperfusion	15% reduction in 72 h AUC- total and 2.0% absolute Increase in the LVEF	Pharmacological cardioprotection
Glucose-insulin-potassium before pPCI (GIK)	IMMEDIATE* (N=357)	Iv GIK infusion for 12 h started by paramedics in ambulance—prior to reperfusion	No difference in progression to MI Reduction in the MI size and less in-hospital mortality and cardiac arrest	Pharmacological cardioprotection **Positive and negative results Only 1 study.**
Metoprolol	METOCARD-CNIC* (N=270)	iv metoprolol three-5 mg boluses administered in ambulance prior to pPCI	Reduction in MI size (5–7 days by CMR)	Pharmacological cardioprotection Inconsistent preclinical data **Only 1 Study.**
Cyclosporine	Piot *et al.** (N=58)	IV CsA (2.5 mg/kg) 10 min prior to PPCI	44% decrease in MI size (72 h AUC total CK) 20% decrease in MI size (CMR in subset of 27 patients) 28% decrease in MI size and smaller LVESV on CMR at 6 months	Pharmacological cardioprotection Two independent clinical trials **Controversial results** Ongoing trials: CIRCUS (NCT01502774) CYCLE (NCT01650662)
	Ghaffari *et al.** (N=101)	IV bolus injection of 2.5 mg/kg of CsA prior to thrombolysis	Administration of CsA show no reduction MI size or any improvement in clinical outcomes	

EXENATIDE STUDIES IN STEMI

Study	N number (Control vs. Exenatide)	Clinical setting	Administration (site of delivery)	Endpoint	Infarct size
Nikolaidis *et al.*[75]	10 vs. 11	AMI and LVEF <40%	72 hr infusion of GLP-1 after primary angioplasty (Hospital)	LVEF improvement (26% in treatment group)	Not Applicable
Lonborg *et al.*[47]	85 vs. 87	STEMI (Thrombolysis and pPCI)	IV 15 min before intervention (Hospital)	Myocardial salvage index (CMR, 90 days)	↓ (23%) ↓ (30%)*[48]
Woo *et al.*[50]	40 vs. 18	STEMI (Thrombolysis and pPCI)	10 µg subcutaneous and intravenous bolus 10 µg 5 min prior to pPCI 10 µg subcutaneous twice per day injection for 2 days (Hospital)	AUC Troponin I CK-MB (72h) CMR (30 days) Echocardiography (6 months)	↓ (46%)
Bernink *et al.*[49]	19 vs. 20	STEMI (Thrombolysis and pPCI)	IV infusion exenatide - 5 µg- started 30 min prior to pPCI continuous infusion for 72h -20 µg/24h- (Hospital)	Safety and feasibility of high dose exenatide	Not Applicable

* Follow-up study to Lonborg *et al.* 2012[47]

Basic Cardiovascular Science

Reperfusion injury in STEMI. Therapeutic opportunities

1. The problem
2. Reperfusion injury after acute coronary occlusion
3. Ischemic conditioning
4. Pharmacological approaches
5. Combination therapy
6. Future research

Combination of RIC + insulin therapy

Rationale of combined therapy

1. Different mechanisms of action, additive efects
2. Lower doses, less side effects
3. Potentially different modulation by age, sex, comorbidities

Selection of treatments

a) Consistent, strong preclinical evidence, as essential previous step to clinical translation.
b) At least two positive and independent proof-of-concept clinical trials.
c) No neutral clinical study.

Combination therapy against myocardial reperfusion injury in PIGS

METHODS

Transient coronary occlusion (40 min, LAD)

Study protocol: 3 treatments

A) RIC: 5' Isq/5'Rep, Right femoral artery (during ischemia)

B) GIK or **glucose 5% (**from 10 min after ischemia onset)

C) Exenatide (from min 25)

	RIC: Yes	RIC: No
GIK	11	11
Exenatide	11	11
No treatment	11	14

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Alburqueque-Bejar et al. *Cardiovascular Research*, June 4, 2015

Combination therapy against myocardial reperfusion injury in PIGS

METHODS

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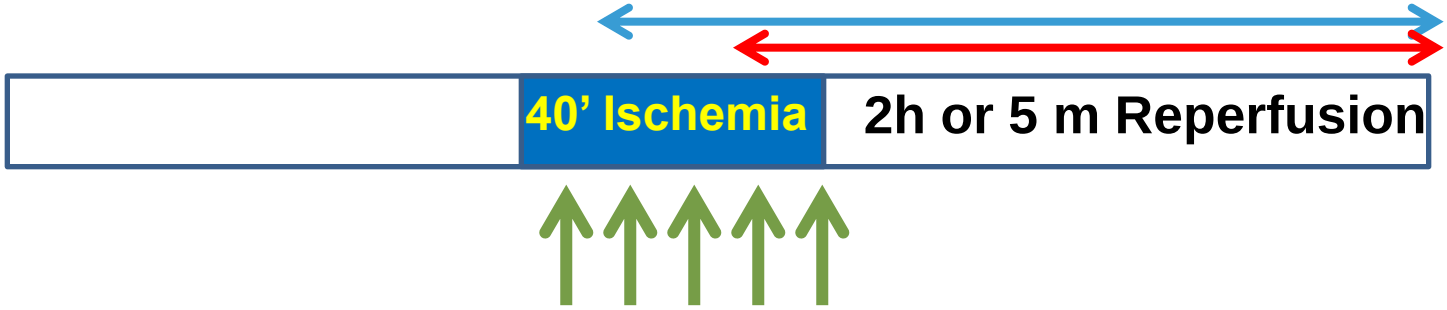


GIK: 30% glucose, 50 U/L insulin, 80 mEq KCl: 1.5 ml/kg

(IMMEDIATE: JAMA 2012)

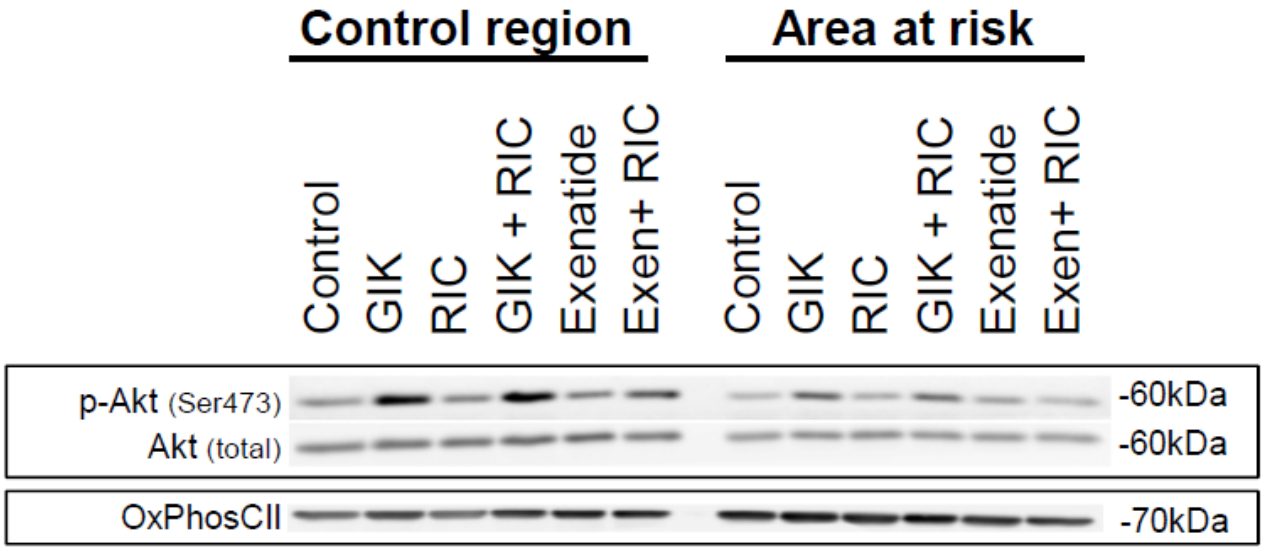
Exenatide (10µg or 40µL of Byetta 10 in 100mL of saline)

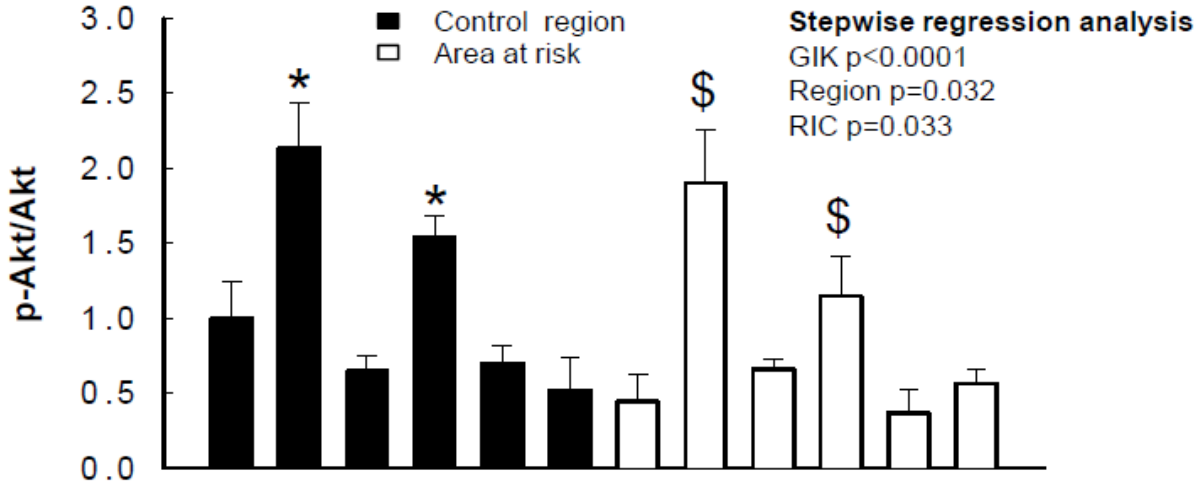
72mL/h 15' before reperfusion

26mL/h since reperfusion, during 2 hours.

(Lonborg et al EHJ 2012)

Signaling pathways. 5 min reperfusion (n=4 per group)





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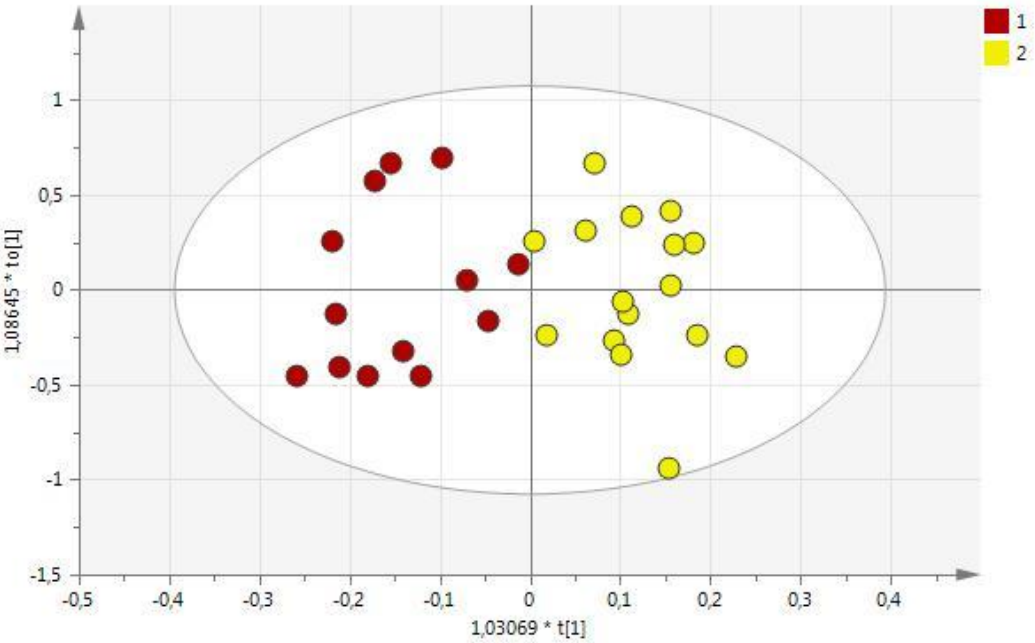
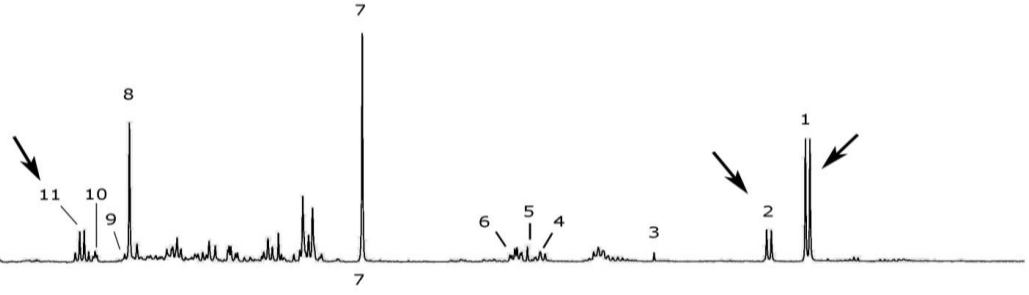
Signaling: H1 NMR metabolomics in **myocardium**

A) Pattern recognition

- **Control**

  Vs
- **GIK or exenatide**





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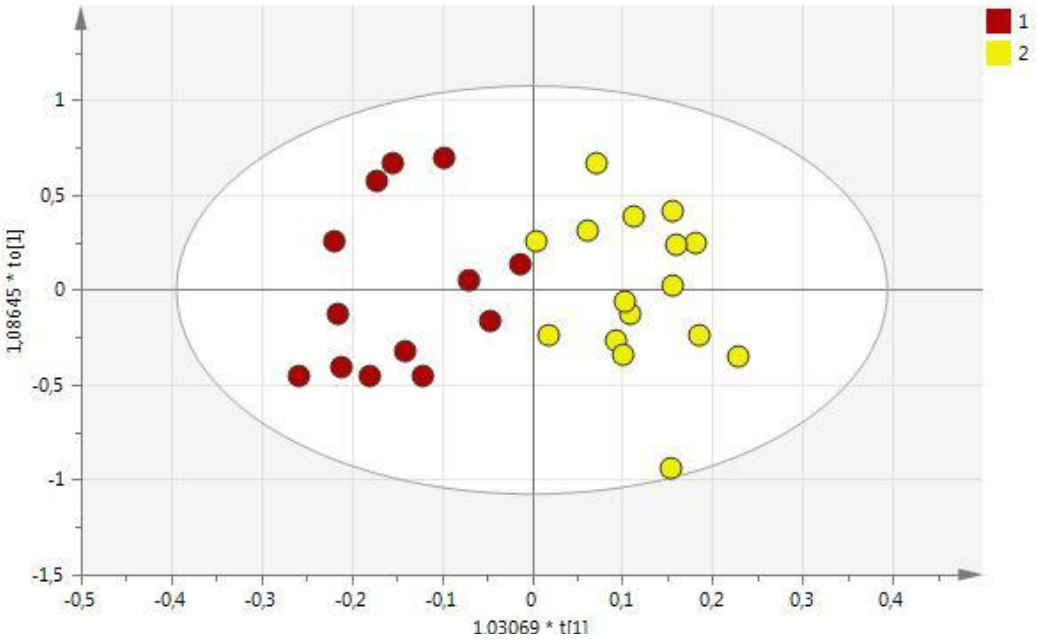
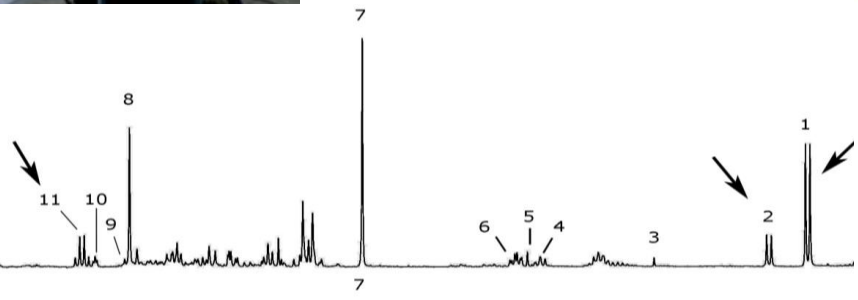
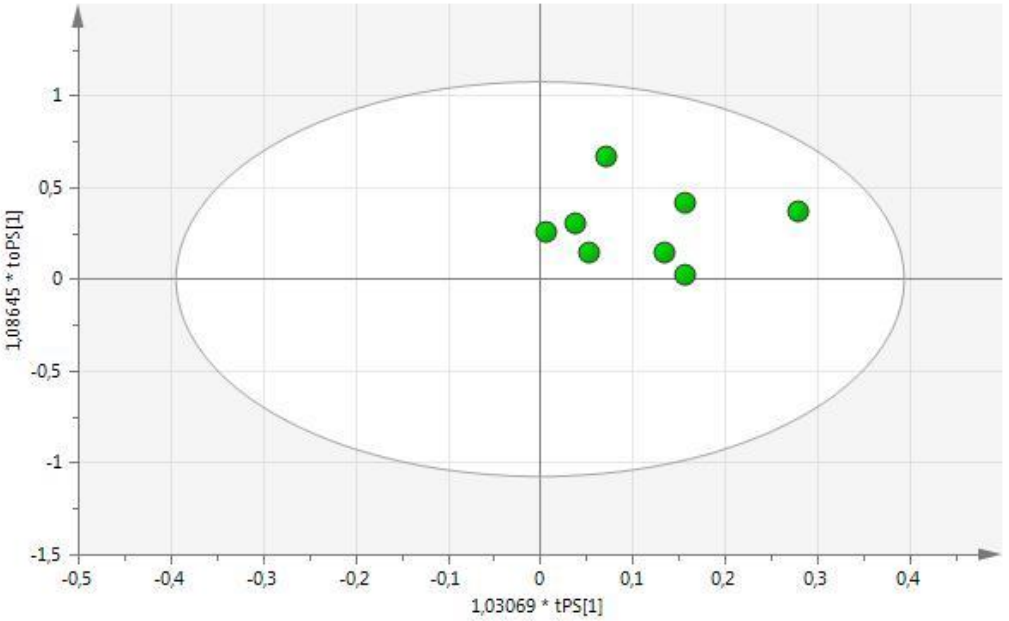


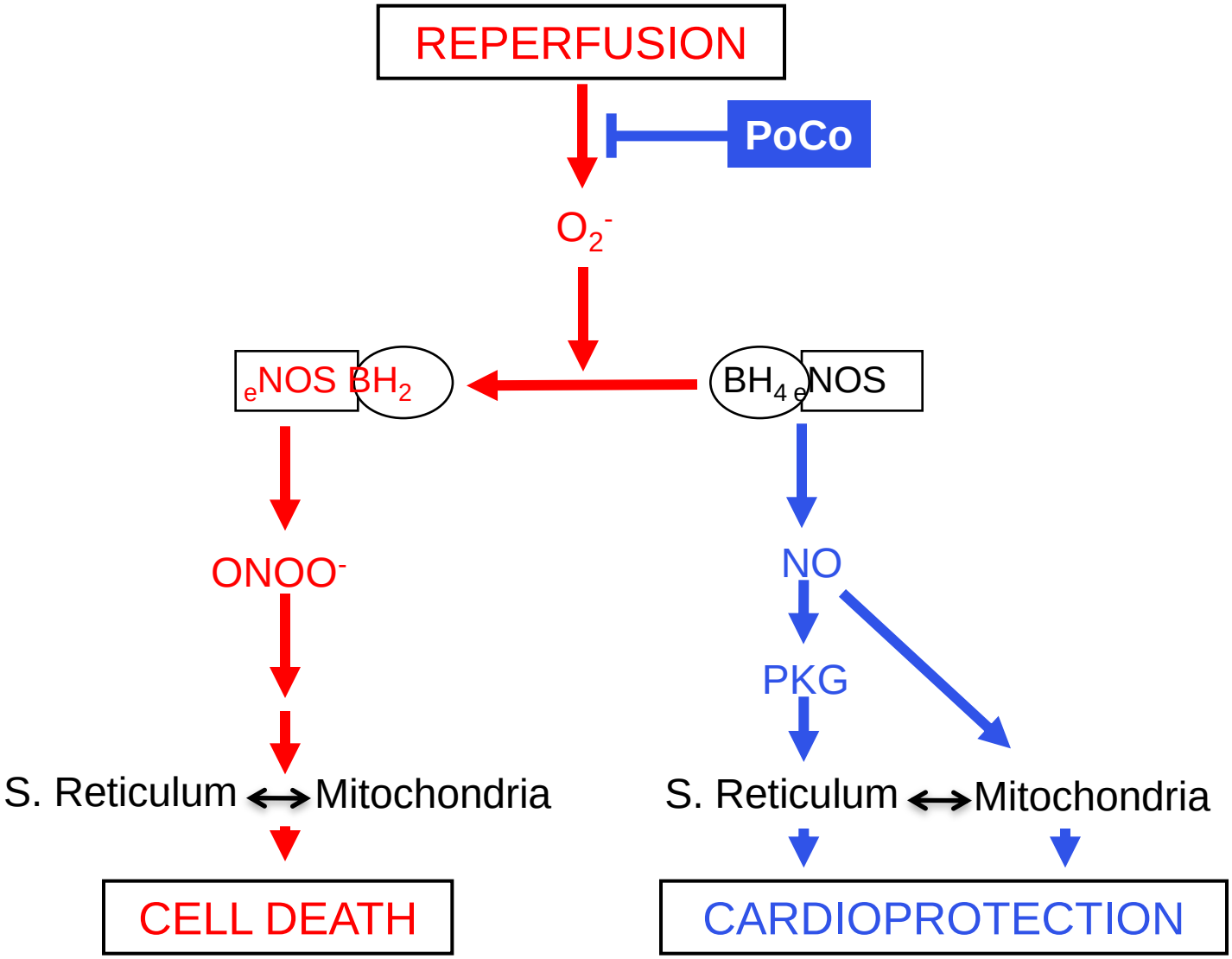
B) Validation:

- RIC





Signaling pathways: AKT – eNOS activation with GIK



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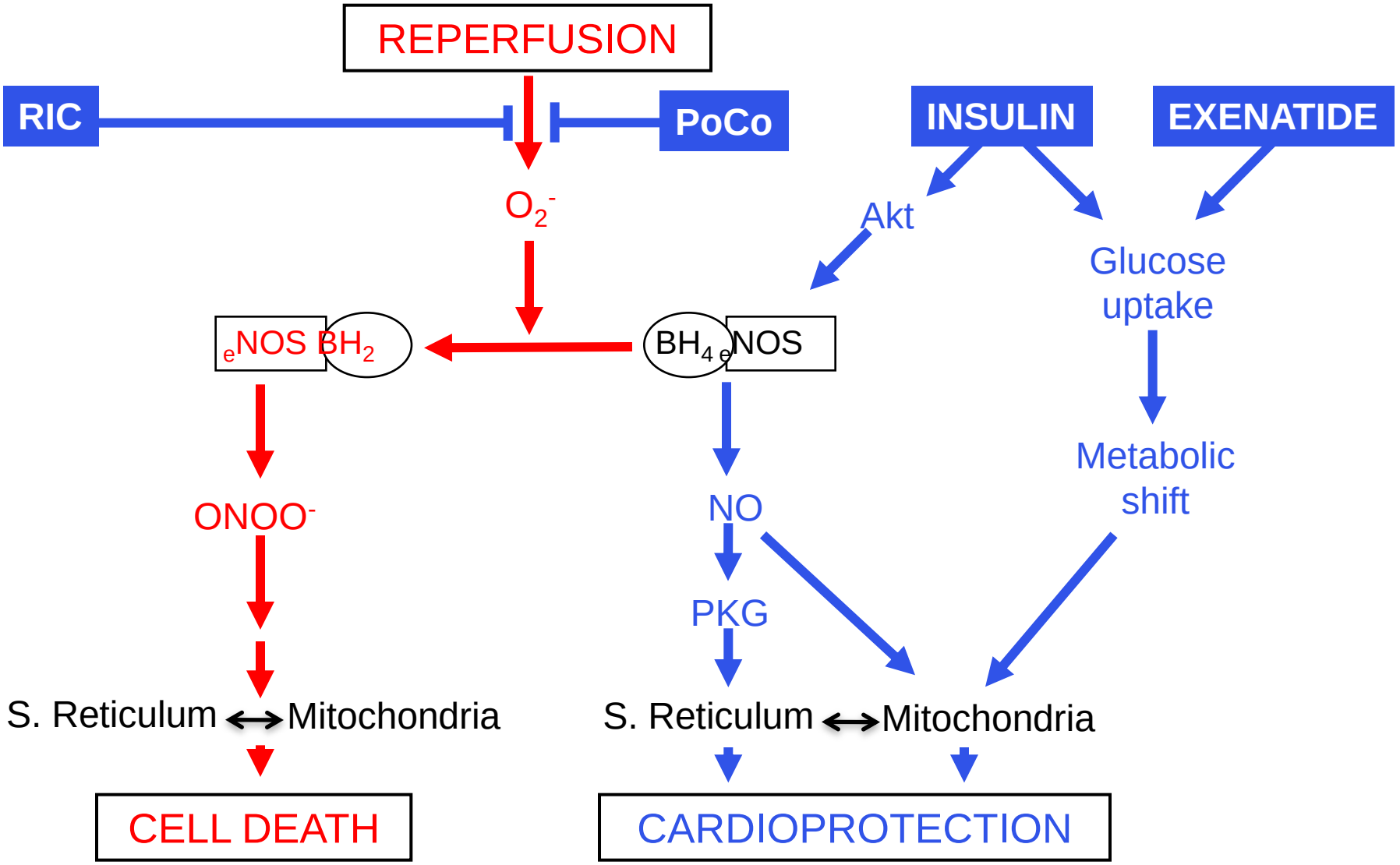
Signaling pathways: different in RIC, GIK and EXE



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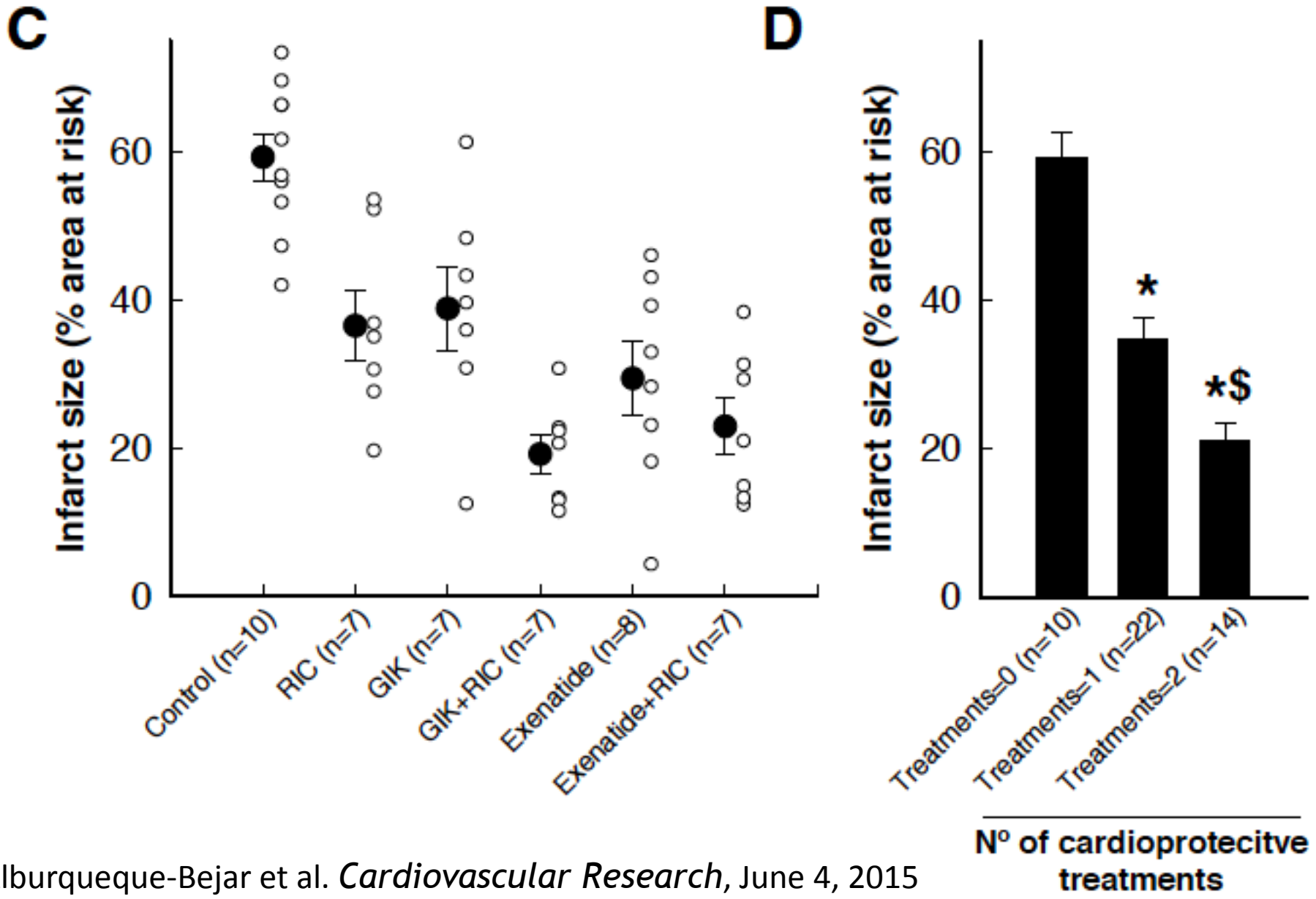
RESULTS: INFARCT SIZE

2 hours of reperfusion (n= 7-10 per group)



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COMBinAtion Therapy in Myocardial Infarction: The COMBAT-MI Trial

ClinicalTrials.gov NCT 04376

SPONSOR:	H.U. Vall d'Hebron Research Institute, Spain
PARTICIPANTS:	HUVH, Barcelona; HUGTP, Barcelona; Spain Hatter Cardiovascular Institute, London, GB
TREATMENTS:	Exenatide i.v., RIC, both or neither

PATIENTS:	Included > 16y with STEMI receiving pPCI < 6h Excluded confused, TIMI > 1, Shock > 48h, c.i. CMRI
Primary ENDPOINT:	Infarct Size (CMRI 2 -7 days after pPCI)
SAMPLE SIZE:	360 pts
DESIGN:	Double blind, placebo controled
STATISTICS:	Factorial 2 x 2
START - END:	Sept 15, 2015 - February 2017

Basic Cardiovascular Science

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Reperfusion injury in STEMI. Therapeutic opportunities

Future research

1) The mechanisms of R-induced cell death are only partially understood
2) The mechanism of RIC needs to be elucidated
3) PKG interventions need to be further explored in IS trials
4) Combination therapies to be developed and clinically tested
5) Extending reduction of RI into prevention of adverse post-infarct remodeling
6) Translation to clinical outcome trials (death, heart failure)
7) Social need: lot of work for cardiovascular scientists and clinical investigators

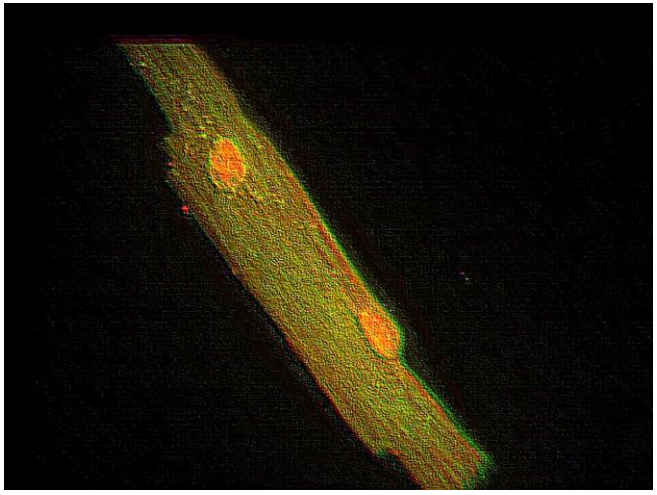
Reducing **M**yocardial **In**jury Secondary to Coronary Artery **D**isease (**REMIND**)

Program 2, Cardiovascular Research Network of the ISCiii

Coordinating group: Sevicio de Cardiología HUVH-VHIR, UAB

VHIR cardiovascular cooperative project

Neurovascular, Diabetes, Hepathology, Nephrology



Program 2 of the Red Cardiovascular del ISCiii
Atherothrombosis/Myocardial Ischemia

MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

AGAUR

Pierre Fabre

Fundació La Marató de TV3

GOBIERNO DE ESPAÑA

MINISTERIO DE CIENCIA E INNOVACIÓN

SEVENTH FRAMEWORI PROGRAMME

PROMISE IRTG GIESSEN BARCELONA

Vall d'Hebro Hospital

Vall d'Heb Institut de Rec

UAB Universitat Autònoma de Barcelona

THANK YOU!

Cardiovascular Research Group
Vall d'Hebron University Hospital and Research institute
Universitat Autònoma de Barcelona. SPAIN