

Assessing the Promise of Remote Conditioning: *New Clinical Developments*

Adaptive Responses in Biology and
Medicine - April 2014



Fondation Leducq

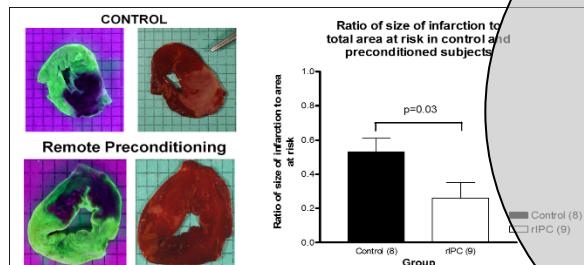
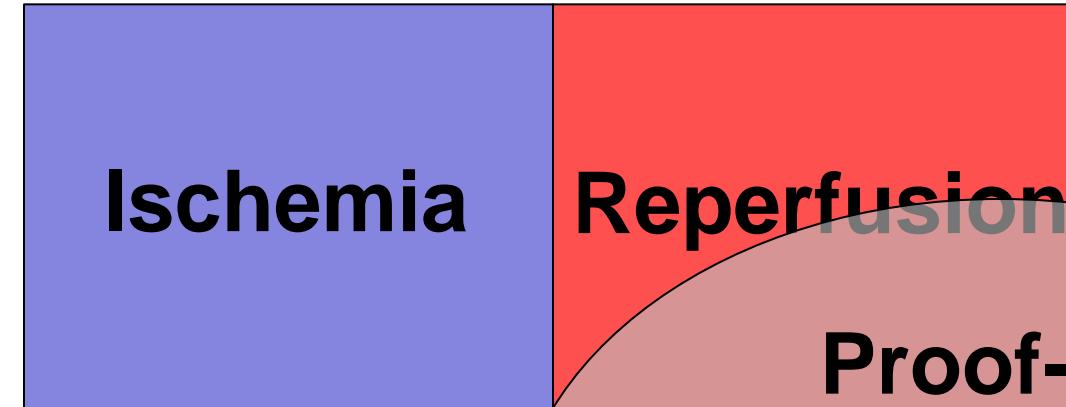
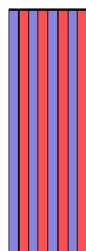
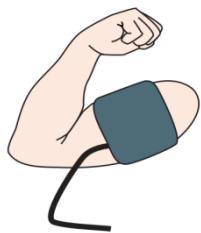
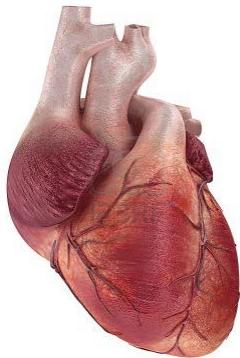


Disclosure

Co-Founder and Shareholder in *CellAegis*, a company developing IP directed towards automated preconditioning devices



Patterns of protection



**Proof-of-
Principle RCT's**
Cardiac Surgery
Coronary Angioplasty
Contrast nephropathy
Renal Tx

Remote ischemic preconditioning

Applications: Cardiac surgery

37 patients, randomised, double blind

Troponin release

Lung function

P=0.004

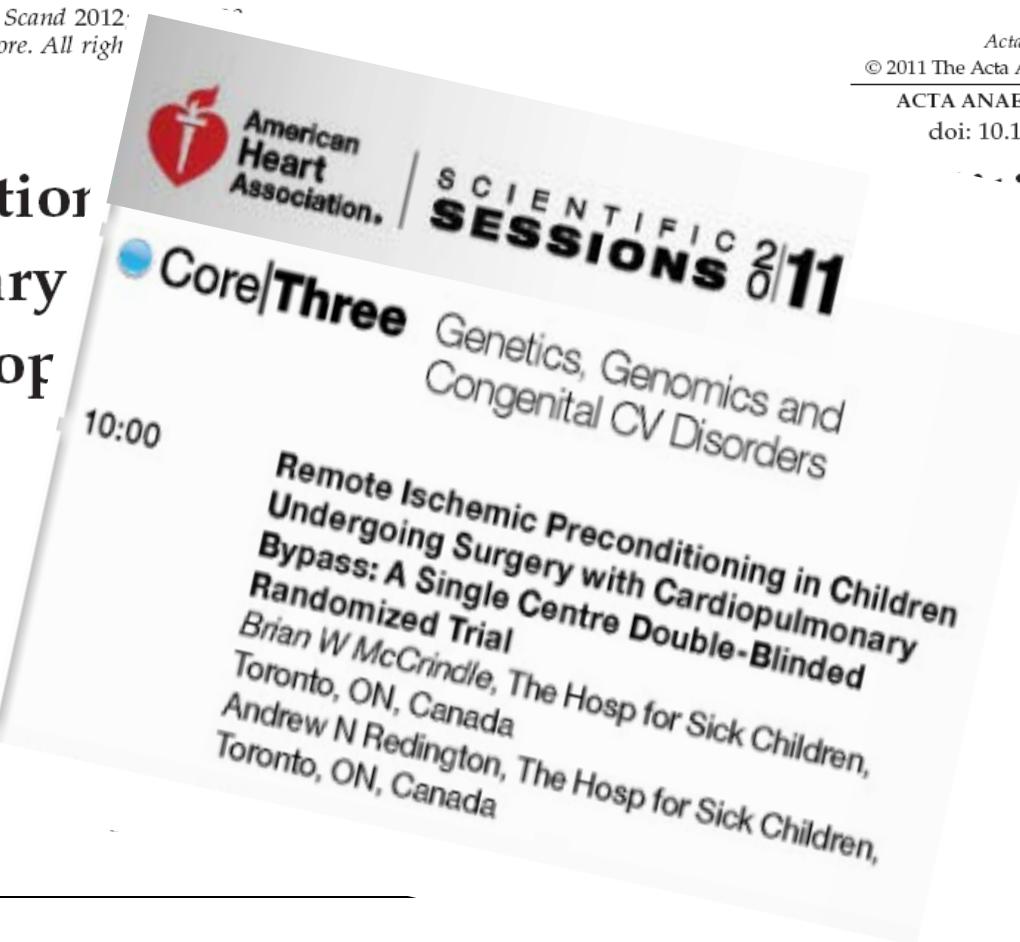
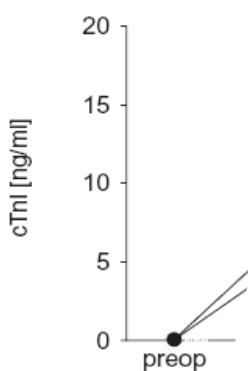
IPC
Control

Cheung et al. JACC 2006

Signaling – Peripheral

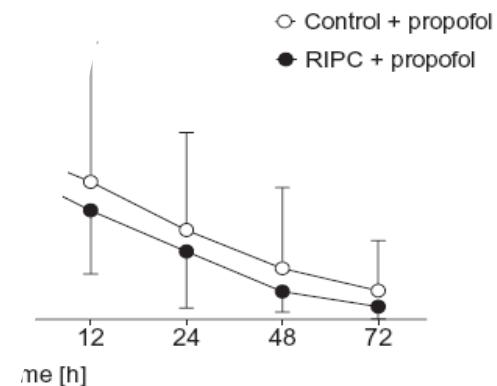
Acta Anaesthesiol Scand 2012;
Printed in Singapore. All righ

Protection
coronary
not prof



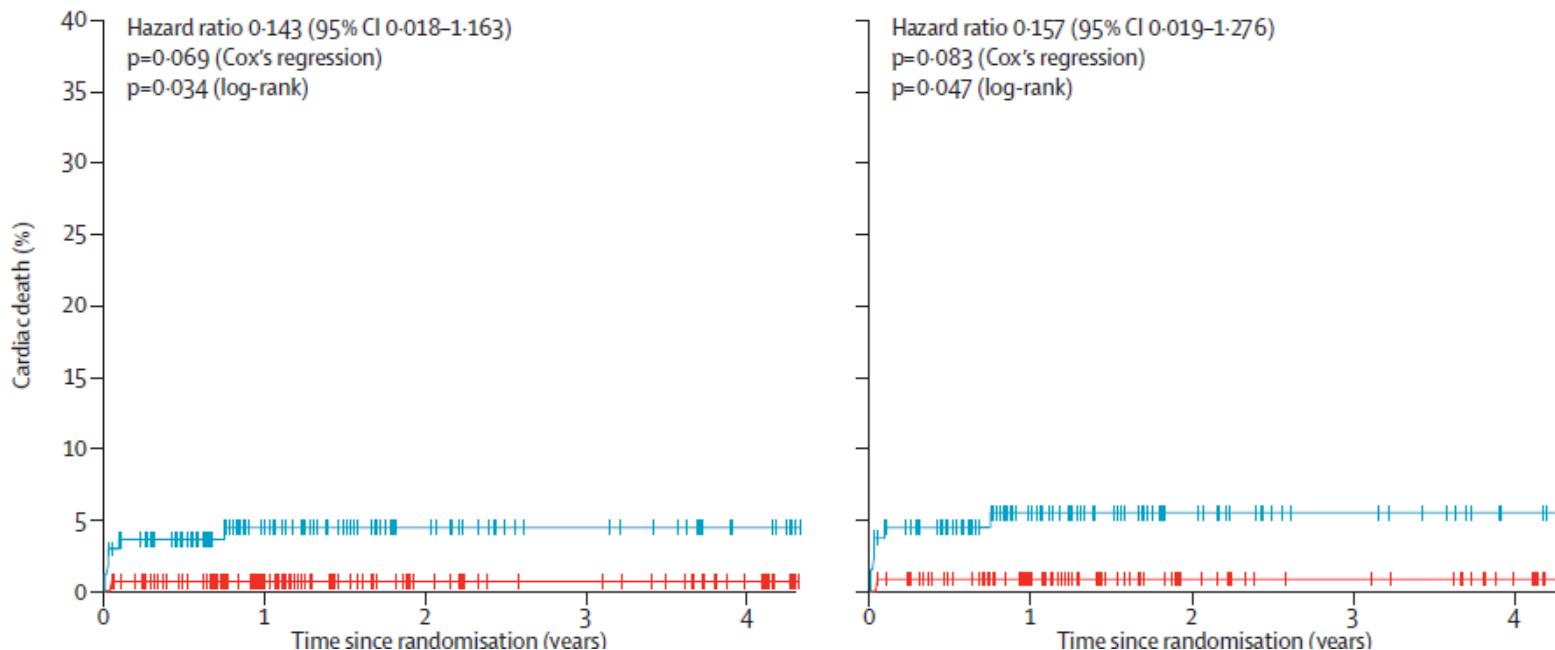
© 2011 The Authors
Acta Anaesthesiologica Scandinavica
© 2011 The Acta Anaesthesiologica Scandinavica Foundation
ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2011.02585.x

...ning during
urane but



Applications: Cardiac surgery

Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial



Applications: Cardiac surgery

Remote Ischemic Preconditioning Preserves Mitochondrial Function and Influences Myocardial MicroRNA Expression in Atrial Myocardium During Coronary Bypass Surgery

Katrine Hordnes Slagsvold, Øivind Rognmo, Morten Høydal, Ulrik Wisløff, Alexander Wahba

Rationale: Remote ischemic preconditioning (RIPC) has been suggested to induce cardioprotection during cardiac surgery. Maintaining proper atrial function is imperative in preventing arrhythmia and thrombus formation. Mitochondria have been proposed as key targets in conveying RIPC mechanisms and effects. MicroRNA (miR) is emerging as an important regulator of mitochondrial function, arrhythmia, and protection from ischemia and reperfusion.

Objective: This study aimed to evaluate the effect of RIPC on mitochondrial respiration and miR expression in human atrial tissue.

Methods and Results: Sixty patients undergoing coronary artery bypass graft surgery were randomized to RIPC (n=30) or control (n=30). RIPC was performed preoperatively by inflating a blood pressure cuff on the upper arm to 200 mm Hg for 3×5 minutes, with 5 minutes reperfusion intervals. Biopsies were obtained from the right atrial appendage before and after aortic cross-clamping. Mitochondrial respiration was measured *in situ* and miR assessed by commercial miR array and quantitative reverse transcription polymerase chain reaction. Postoperative atrial fibrillation occurrence was monitored by biotelemetry. Maximal mitochondrial respiration was preserved throughout surgery after RIPC but significantly reduced ($-28\% ; P<0.05$) after aortic cross-clamping in control. Incidence of postoperative atrial fibrillation was lower after RIPC versus control (14% versus 50%; $P<0.01$). Myocardial expression of miR-133a and miR-133b increased after aortic cross-clamping in both RIPC and control, whereas miR-1 was upregulated in control only. MiR-338-3p expression was higher in RIPC versus control after aortic cross-clamping.

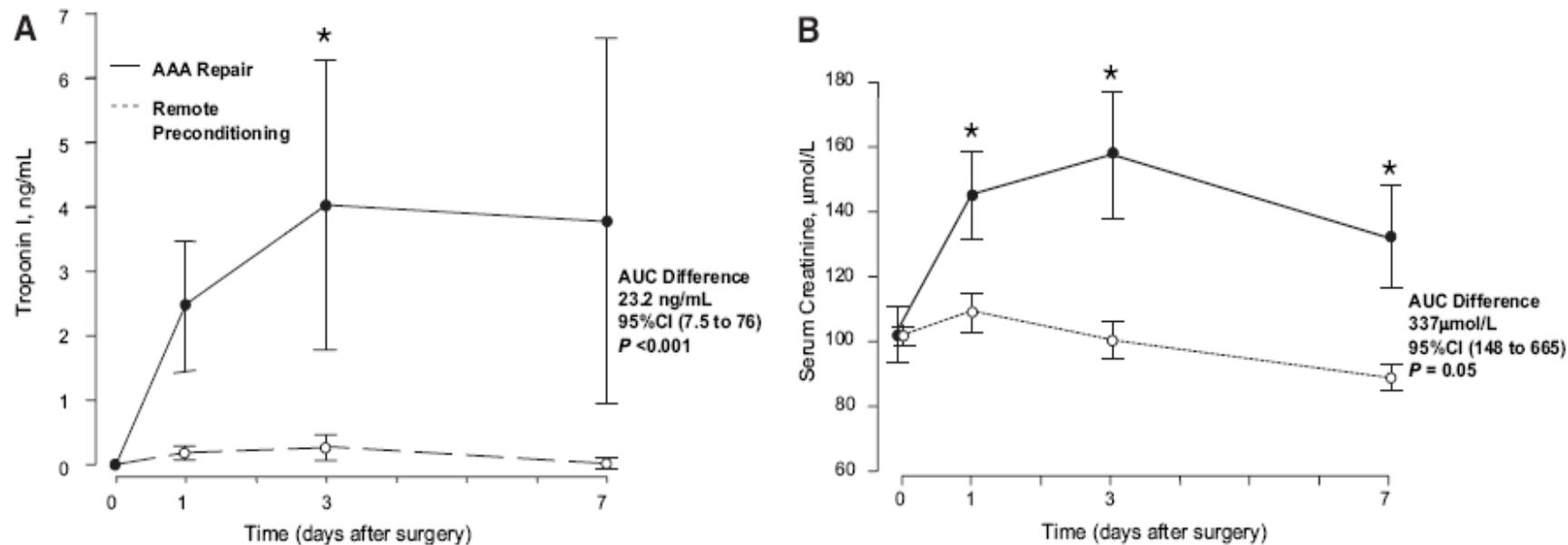
Conclusions: RIPC preserves mitochondrial respiration and prevents upregulation of miR-1 in the right atrium during coronary artery bypass graft.

POST-OP AF

- 50% Controls
 - 14% RIPC
- p<0.01

Applications: AAA Surgery

- Postop MI reduced from 39% to 12%, P=0.005
- Postop renal dysfunction from 30% to 7%, P=0.009



Applications: Elective PCI

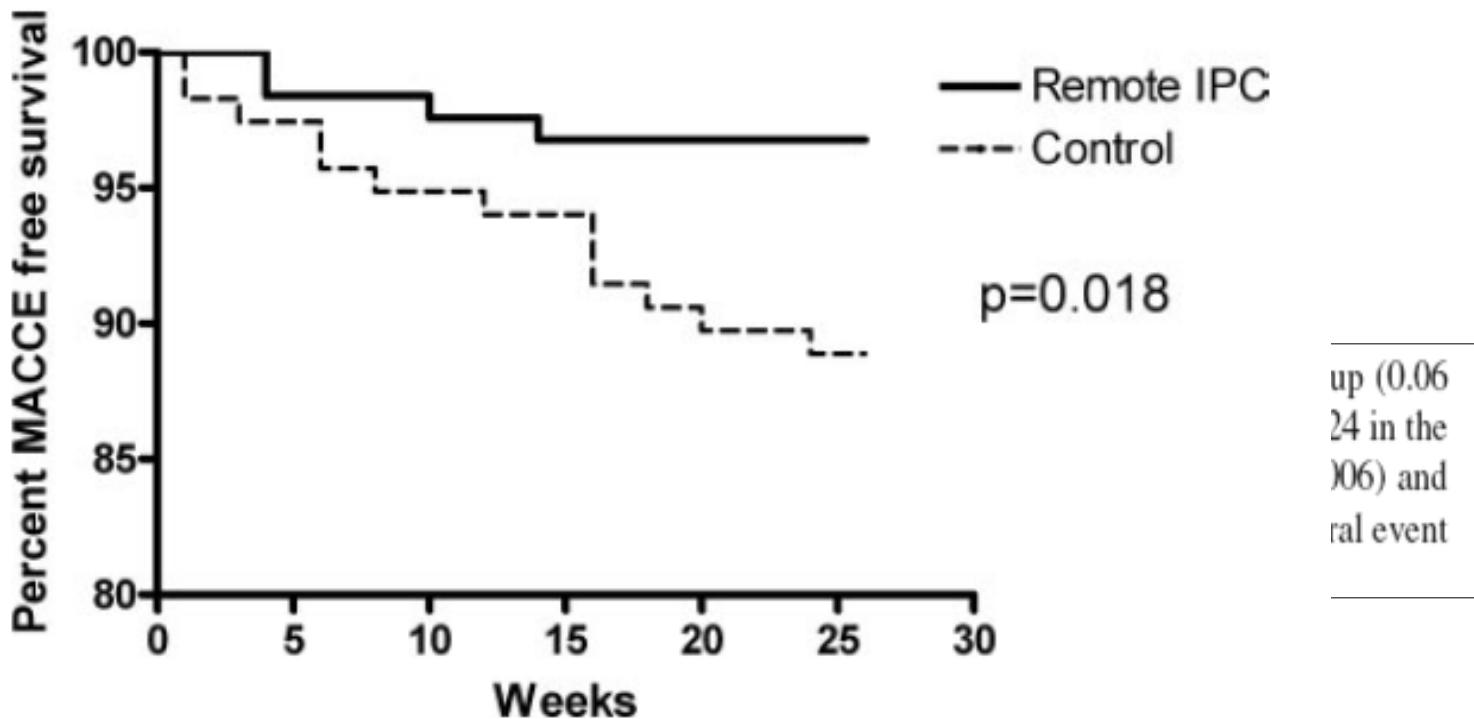
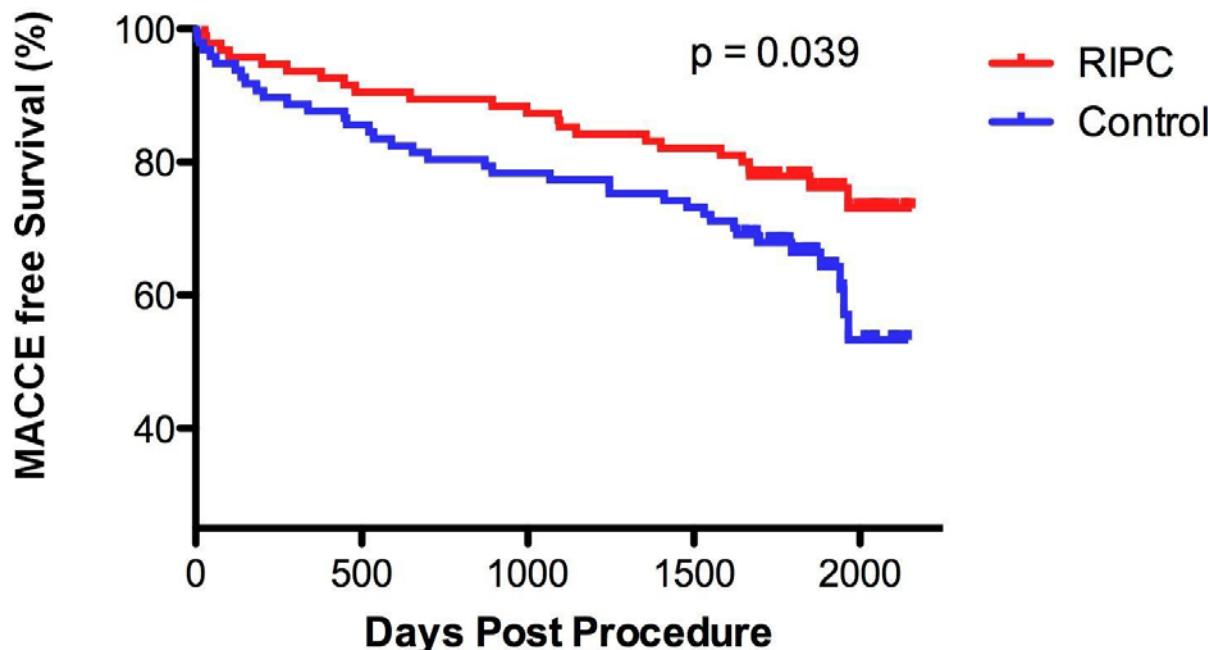


Figure 3. Kaplan-Meier graph of the MACCE rate at 6 months after PCI in the 201 patients with complete data (104 in the IPC group, 97 in the control group).

Applications: Elective PCI

Remote Ischemic Preconditioning Improves Outcome at 6 Years After Elective Percutaneous Coronary Intervention

The CRISP Stent Trial Long-term Follow-up

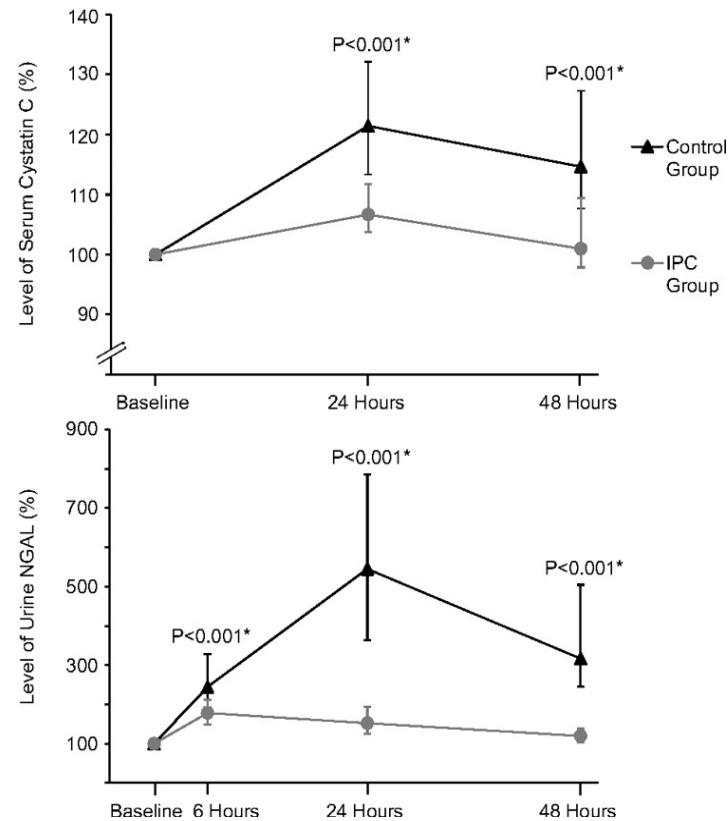
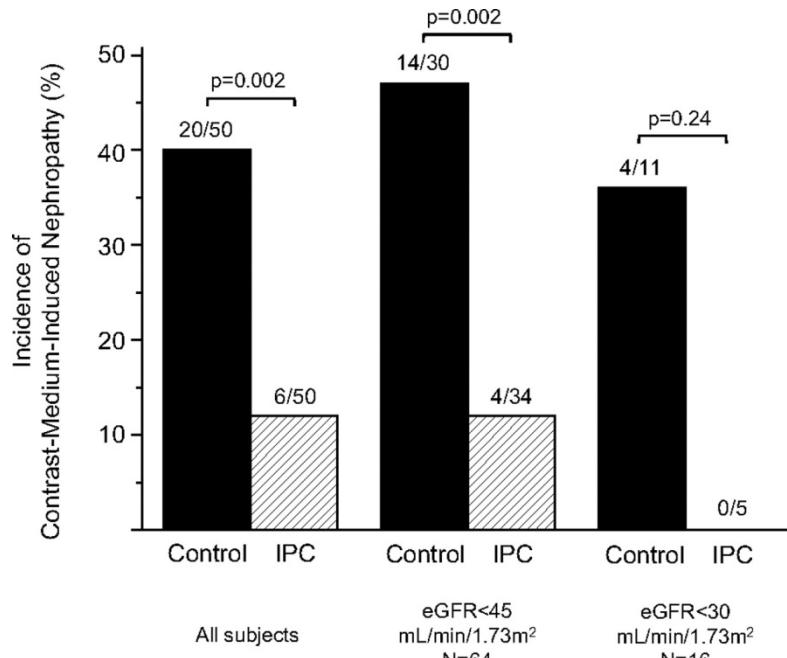


Applications: Contrast nephropathy

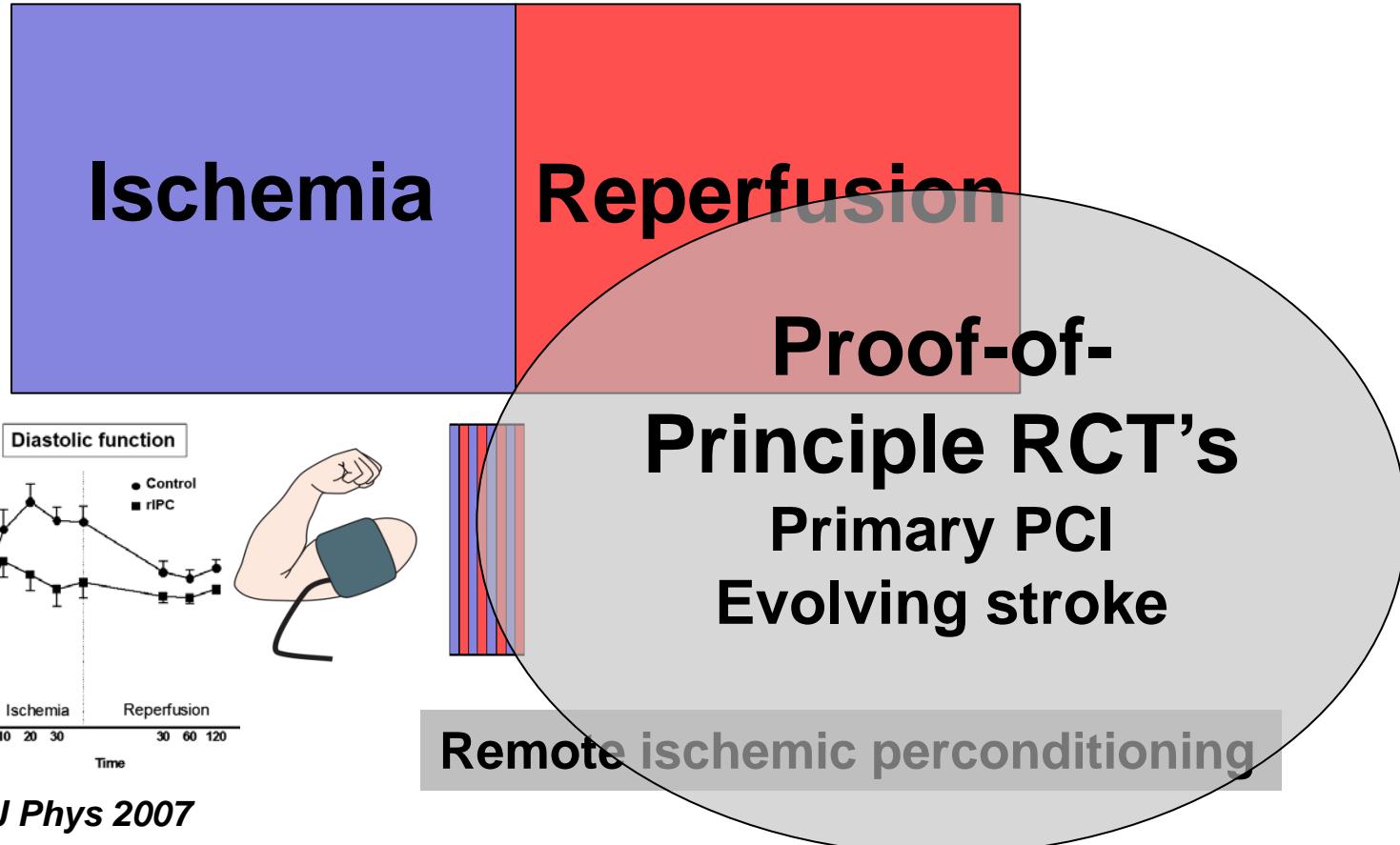
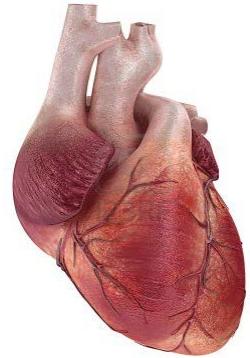
Ischemic Preconditioning for Prevention of Contrast Medium-Induced Nephropathy

Randomized Pilot RenPro Trial (Renal Protection Trial)

Fikret Er, MD; Amir M. Nia, MD; Henning Dopp, MS; Martin Hellmich, PhD;
Kristina M. Dahlem, MS; Evren Caglayan, MD; Torsten Kubacki, MD; Thomas Benzing, MD;
Erland Erdmann, MD; Volker Burst, MD*; Natig Gassanov, MD*

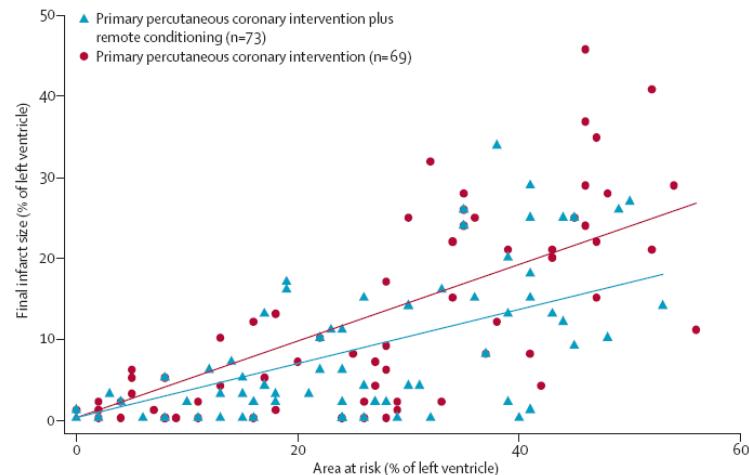
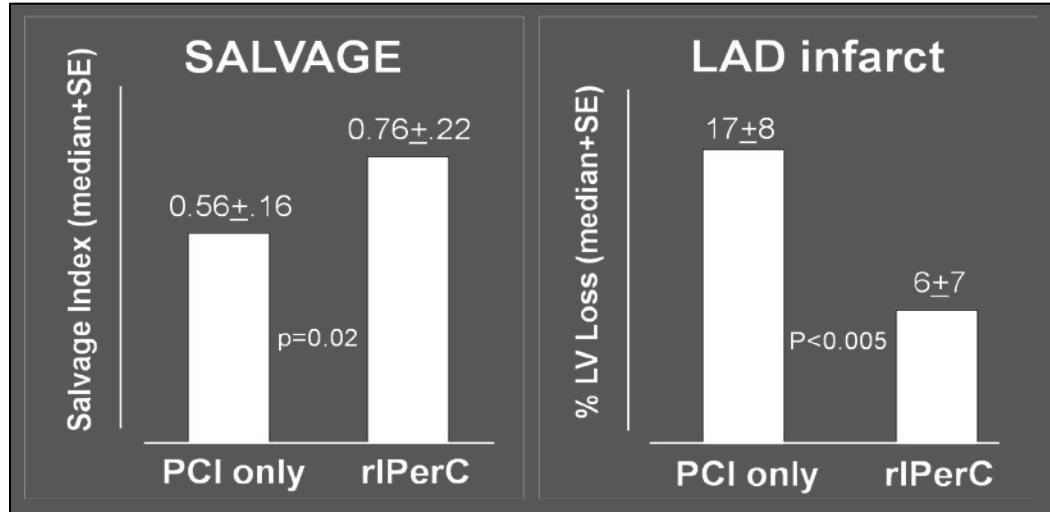


Timing of protection



Schmidt et al. Am J Phys 2007

Applications: Evolving MI

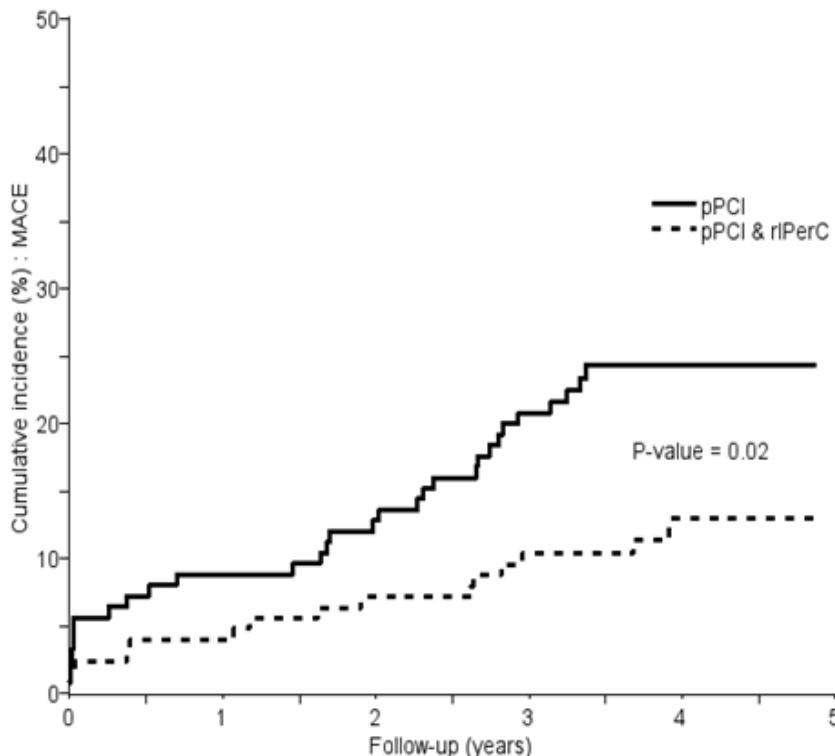


Botker et al. Lancet 2010

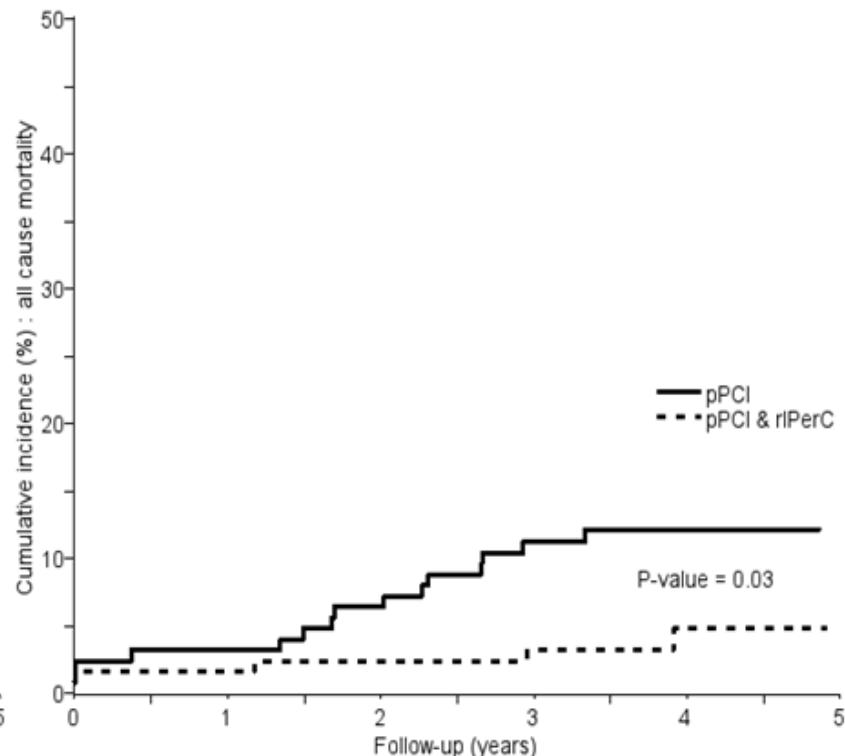
Late outcomes



European Heart Journal (2014) 35, 168–175
doi:10.1093/eurheartj/eht369



FASTTRACK CLINICAL RESEARCH



Neuroprotection

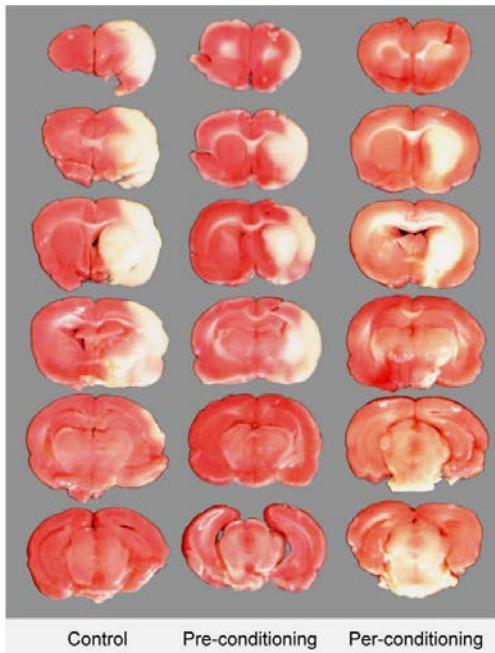


Fondation Leducq

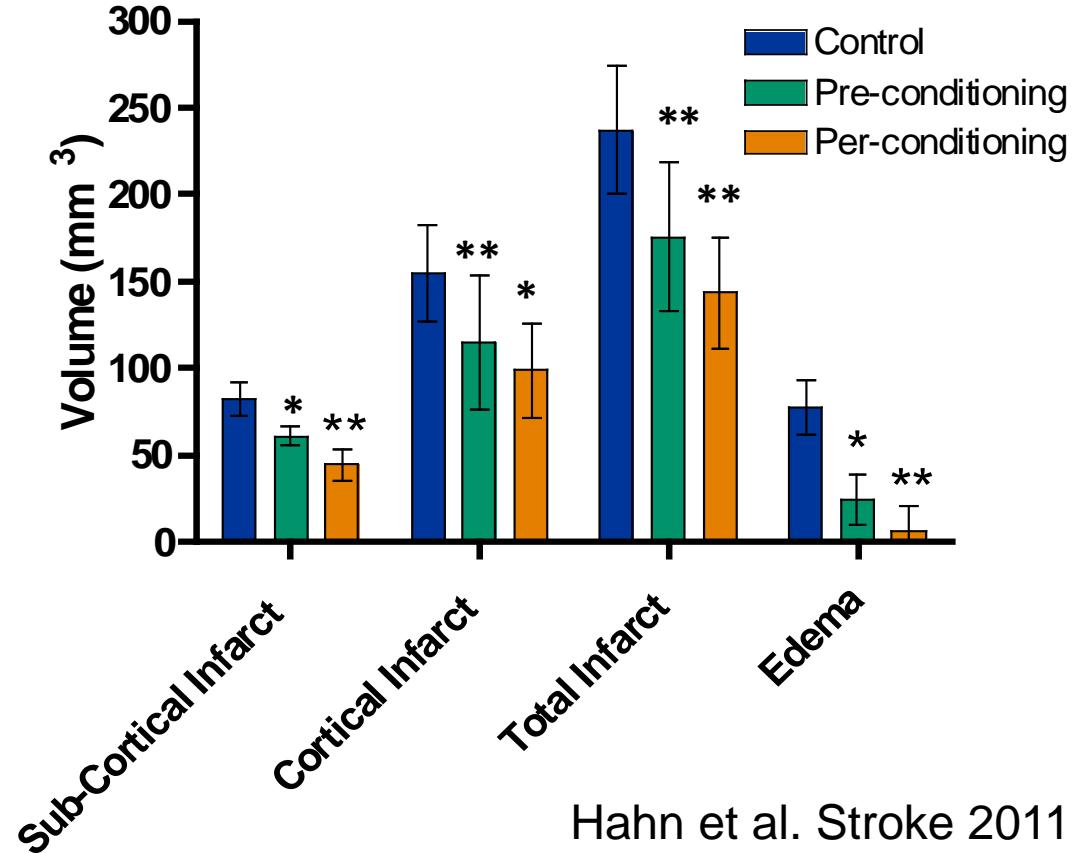


Rat MCAO Model

- 2 hours occlusion
- 24 hours reperfusion



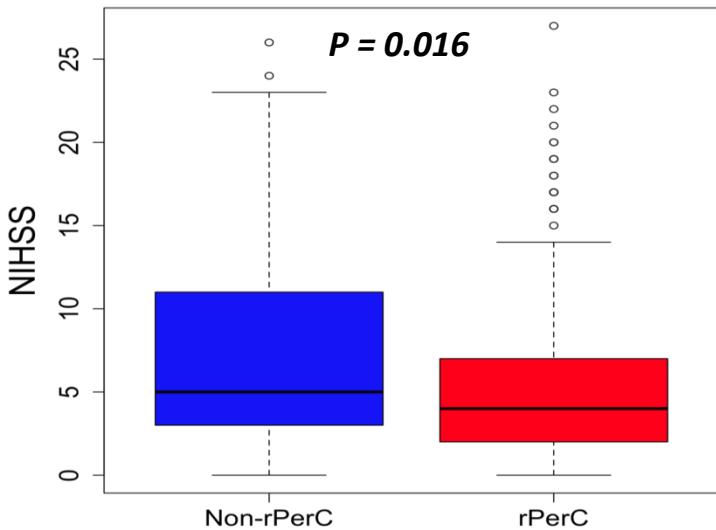
Infarct and Edema Volumes



Hahn et al. Stroke 2011

Thrombolysed Stroke

NIHSS acute (N=285)

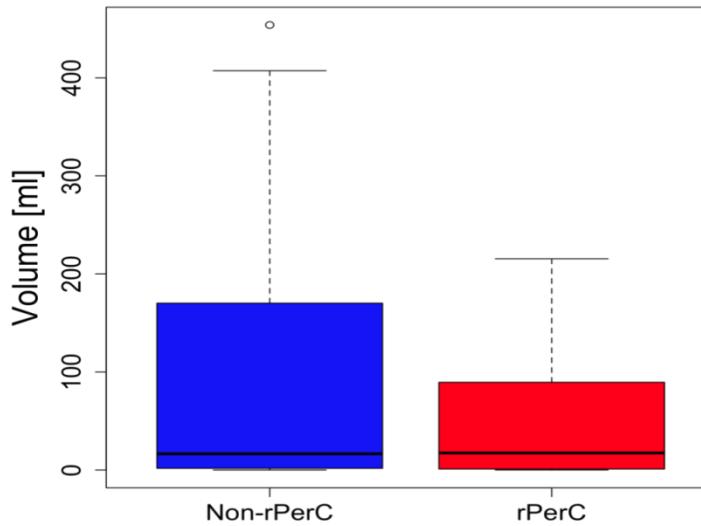


- rPerC: 5 (3;11)

+ rPerC: 4 (2;7)

Median (IQR)

Perfusion-weighted Imaging acute (N=149)



- rPerC: 16.55 ml (1.71;170.16)

+ rPerC: 17.35 ml (1.01;87.18)

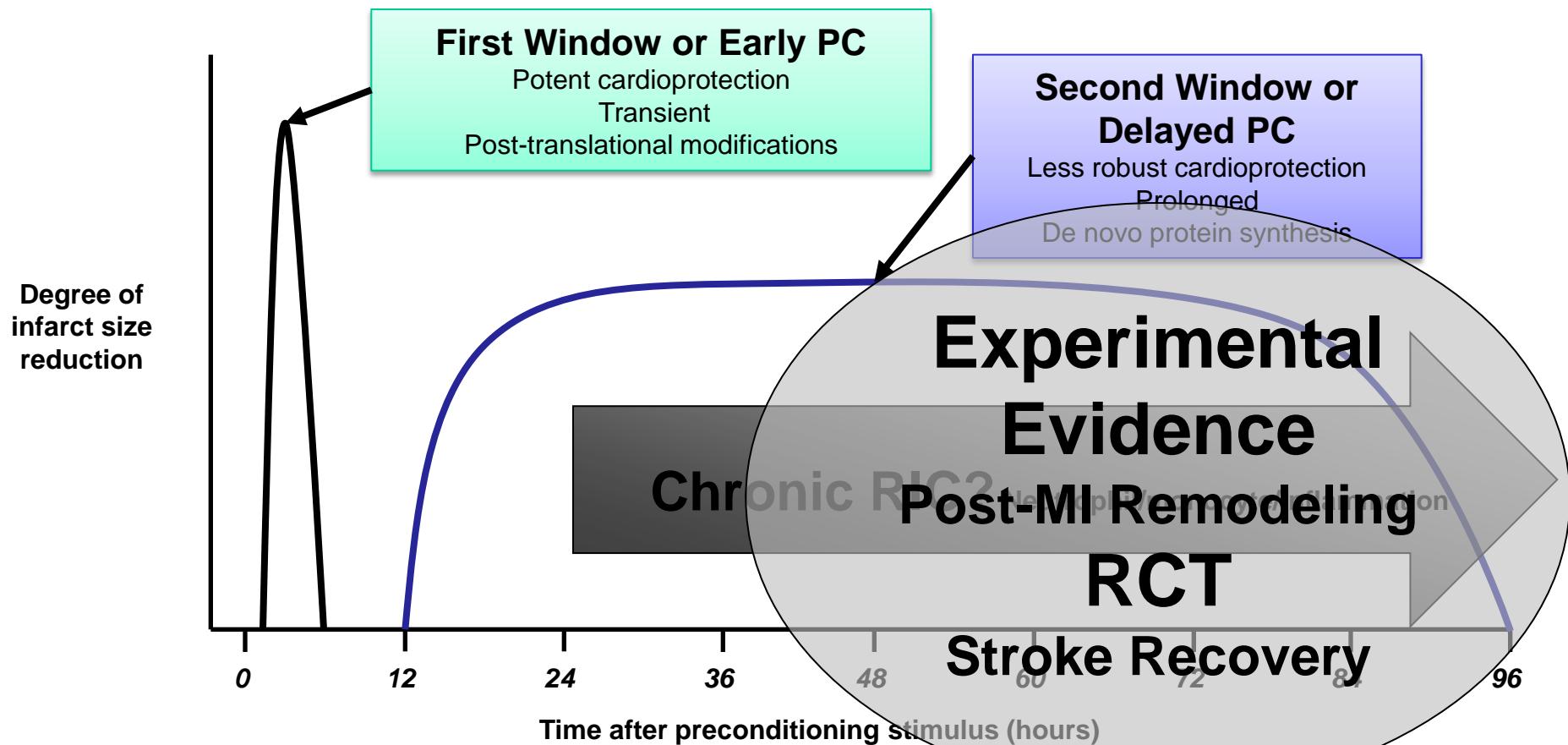
Median (IQR)



The Danish National Research Foundation's
Center of Functionally Integrative Neuroscience
University of Aarhus / Aarhus University Hospital



Patterns of protection



Remote IPC – Genomic responses



TABLE 1. Myocardial gene expression patterns after remote ischemic preconditioning

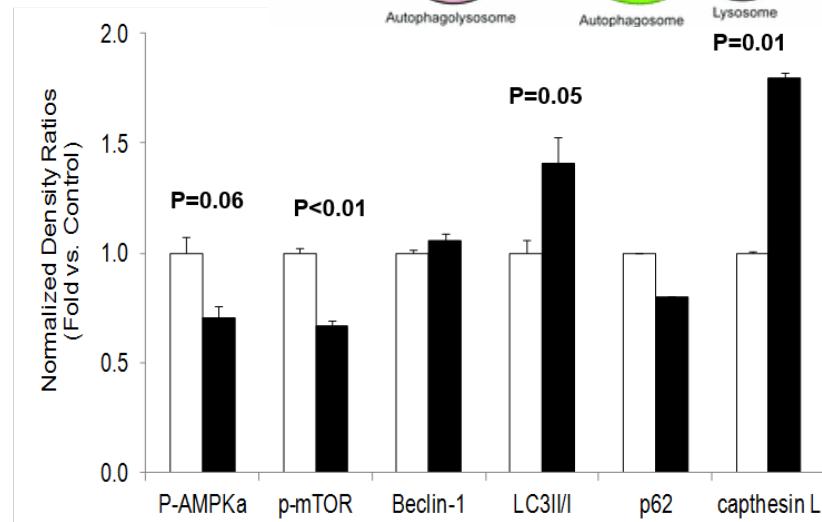
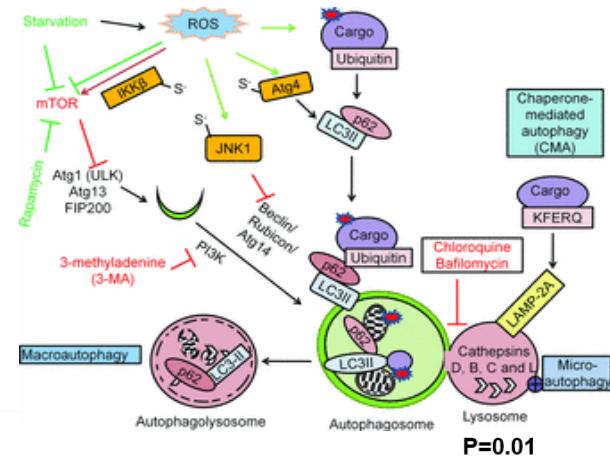
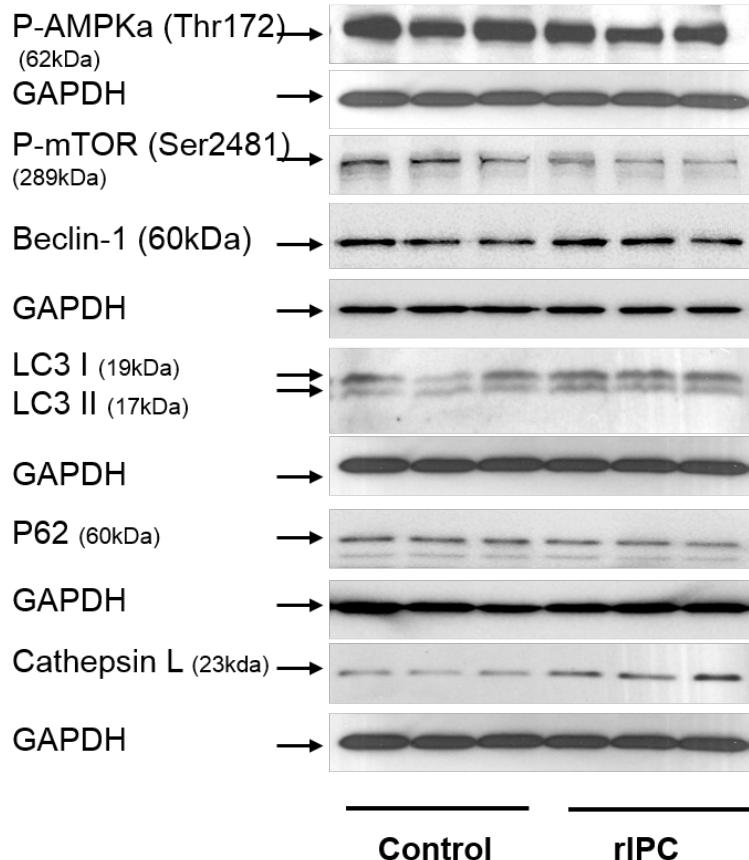
GenBank no.	Affymetrix no.	Gene name	Gene symbol	Group 1 Control, early	Group 2 IPC, early	Group 3 Control, late	Group 4 IPC, late
Immediate early response genes							
NM_007913	1417065	Early growth response 1	Egr-1	0.74 ± 0.32	0.76 ± 0.16	2.82 ± 0.98	1.15 ± 0.17
AV299745	1437850	Cellular nucleic acid–binding protein	Cnbp	0.71 ± 0.16	1.37 ± 0.15	0.85 ± 0.18	1.42 ± 0.39
Phosphatase genes							
NM_013642	1448830	Dual-specificity phosphatase 1	Dusp1	0.88 ± 0.21	0.78 ± 0.16	2.4 ± 0.45	1.14 ± 0.34
NM_026268	1415834	Dual-specificity phosphatase 6	Dusp6	0.69 ± 0.19	0.89 ± 0.18	1.67 ± 0.2	1.25 ± 0.2
BB816770	1456462	Protein phosphatase 1, cb	Ppp1cb	0.81 ± 0.21	1.16 ± 0.3	0.72 ± 0.18	1.35 ± 0.19
Heat shock protein genes							
NM_022310	1416064	Heat shock 70-kd protein 5	Hspa5,Grp78	0.96 ± 0.16	0.75 ± 0.14	2.56 ± 0.87	1.23 ± 0.63
AK010861	1423151	DnaJ (Hsp40) homolog	Dnajb11	0.92 ± 0.16	0.97 ± 0.2	2.96 ± 0.66	1.15 ± 0.33
BC006722	1420622	Heat shock 70-kd protein 8	Hspa8,Hsp73	0.75 ± 0.15	1.77 ± 0.39	0.82 ± 0.23	1.13 ± 0.4
Oxidative stress response genes							
BF319868	1423423	Glucose-regulated protein 58	Grp58	1.04 ± 0.16	0.85 ± 0.14	2.28 ± 0.59	1.16 ± 0.55
NM_016764	1416166	Peroxiredoxin 4	Prdx4	0.72 ± 0.4	1.33 ± 0.39	0.74 ± 0.45	1.4 ± 0.41
BB114220	1436756	L-3-hydroxyacyl-CoA dehydrogenase	Hadhscc	0.4 ± 0.27	1.41 ± 0.2	0.49 ± 0.37	1.35 ± 0.27
NM_00880	1417148	Platelet-derived growth factor receptor	Pdgfrb	1.21 ± 0.35	0.59 ± 0.18	1.08 ± 0.2	0.87 ± 0.25
BC002148	1451263	Fatty acid-binding protein 4	Fabp4	0.67 ± 0.16	1.29 ± 0.18	0.77 ± 0.17	1.36 ± 0.22
Mitochondrial function gene							
AK014590	1418428	Kinesin family member 5B	Kif5b	0.75 ± 0.24	1.53 ± 0.36	0.75 ± 0.26	1.39 ± 0.33
TNF signaling gene							
NM_013749	1418572	TNF receptor 12	Tnfrsf12a	1.86 ± 0.28	1.33 ± 0.8	1.28 ± 0.45	0.62 ± 0.32
Genes with unknown function							
BB483357	1438651	Angiotensin receptor-like 1	Agtr1l	0.71 ± 0.25	0.54 ± 0.18	2.14 ± 0.35	1.38 ± 0.58
AK014338	1428112	Arginine rich	Armet	0.98 ± 0.16	0.79 ± 0.15	6.13 ± 2.4	2.25 ± 1.9
AK018378	1423420	Adrenergic receptor, β 1	Adrb1	0.6 ± 0.26	1.14 ± 0.24	1.04 ± 0.52	1.21 ± 0.41
NM_02638	1416187	DNA segment, Chr4	D4Bwg05	0.68 ± 0.17	1.46 ± 0.2	0.68 ± 0.18	1.46 ± 0.23

IPC, Ischemic preconditioning; CoA, coenzyme A; TNF, tumor necrosis factor.

RIPC - Autophagy



10-Days repeated RIC



Signaling – Reperfusion injury

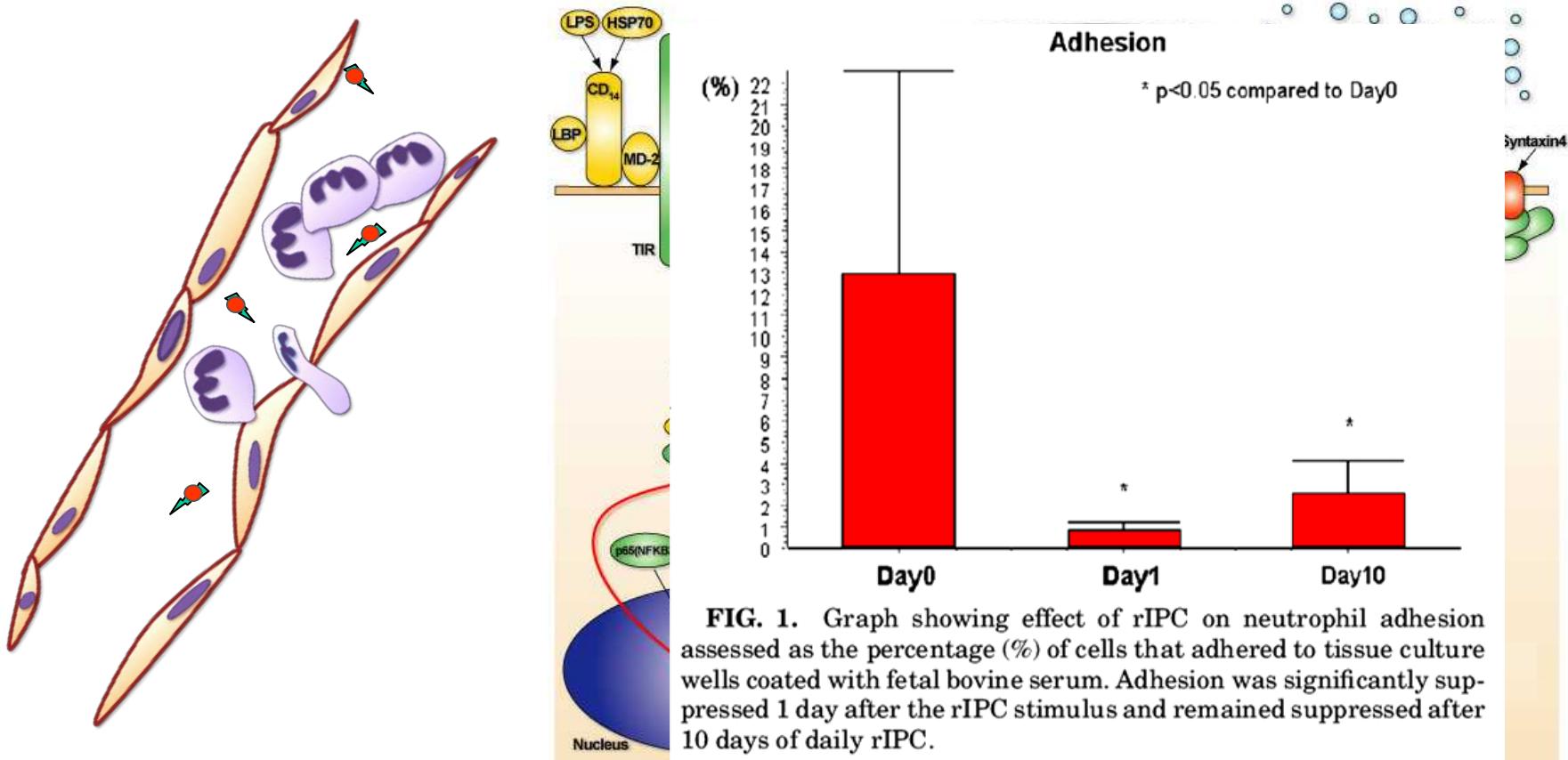
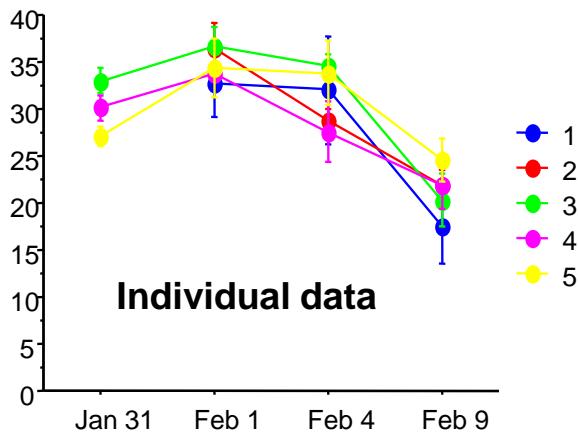
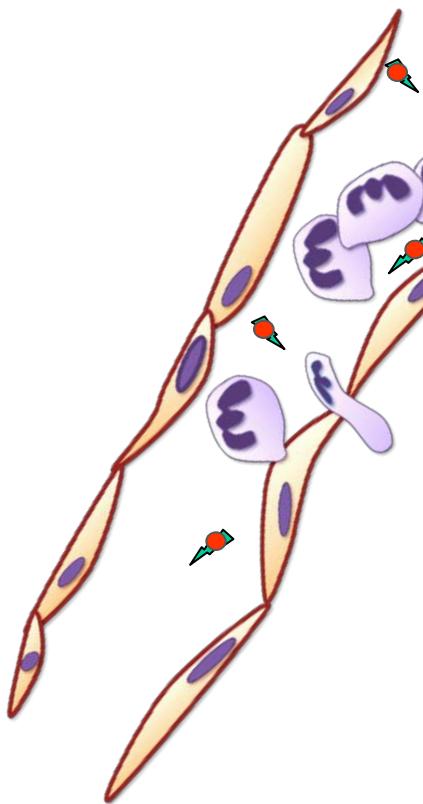


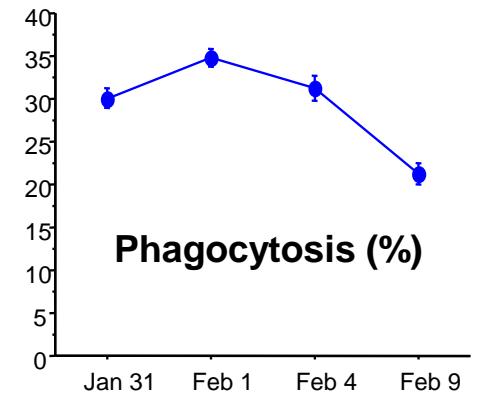
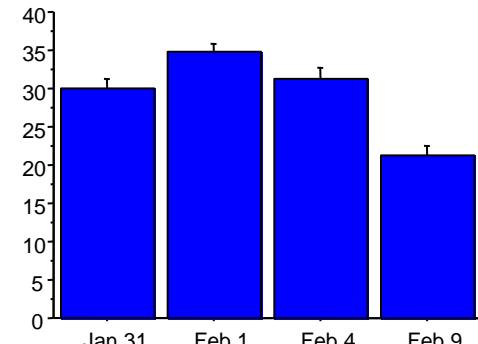
FIG. 1. Graph showing effect of rIPC on neutrophil adhesion assessed as the percentage (%) of cells that adhered to tissue culture wells coated with fetal bovine serum. Adhesion was significantly suppressed 1 day after the rIPC stimulus and remained suppressed after 10 days of daily rIPC.

Signaling – Reperfusion injury



Paired t-test
Hypothesized Difference = 0

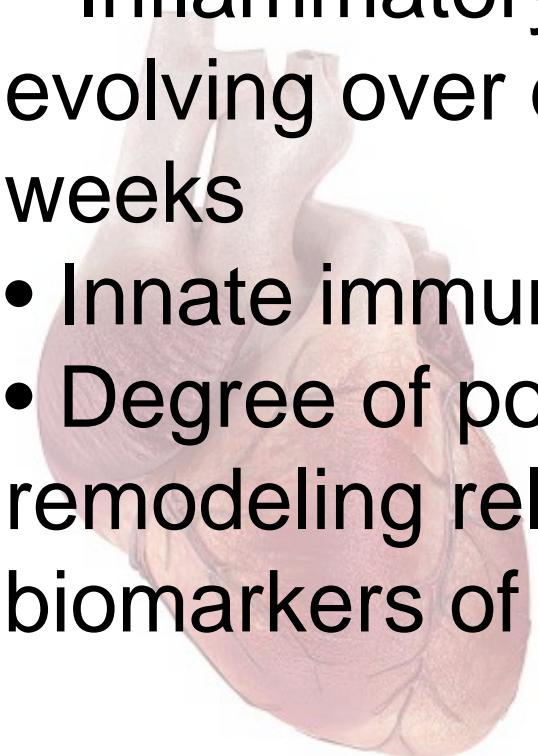
	Mean Diff.	DF	t-Value	P-Value
Jan 31, Feb 1	-4.837	5	-2.955	.0317
Jan 31, Feb 4	-1.875	5	-.824	.4475
Jan 31, Feb 9	7.850	5	3.599	.0156
Feb 1, Feb 4	3.466	9	1.626	.1384
Feb 1, Feb 9	13.587	9	9.377	<.0001
Feb 4, Feb 9	10.121	9	4.937	.0008



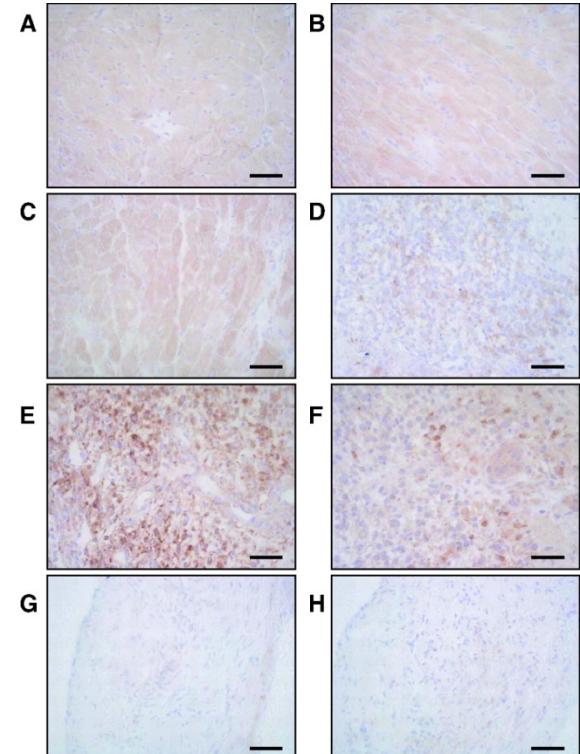


Post-MI Remodeling

- ‘Inflammatory’ process evolving over days and weeks
- Innate immune system
- Degree of post MI remodeling relates to biomarkers of inflammation



Toll-Like Receptor 4 Mediates Maladaptive Left Ventricular Remodeling and Impairs Cardiac Function After Myocardial Infarction

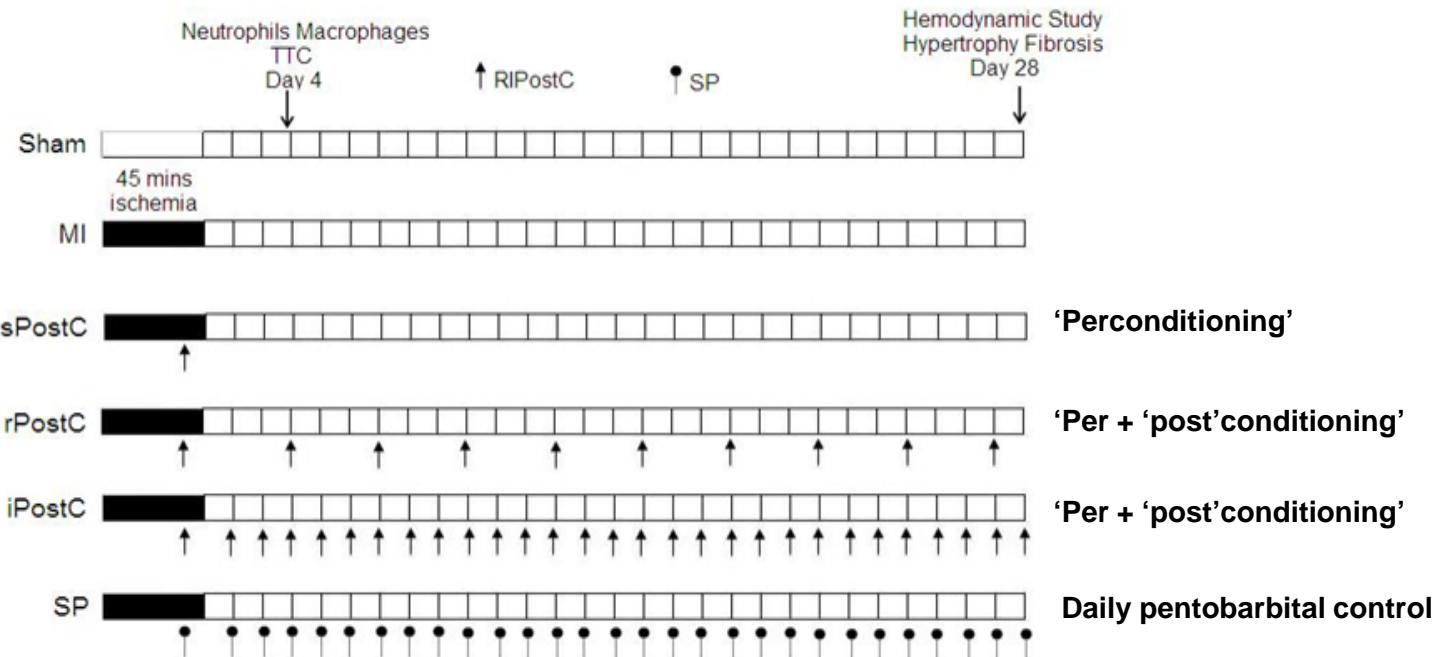




Post-MI Remodeling

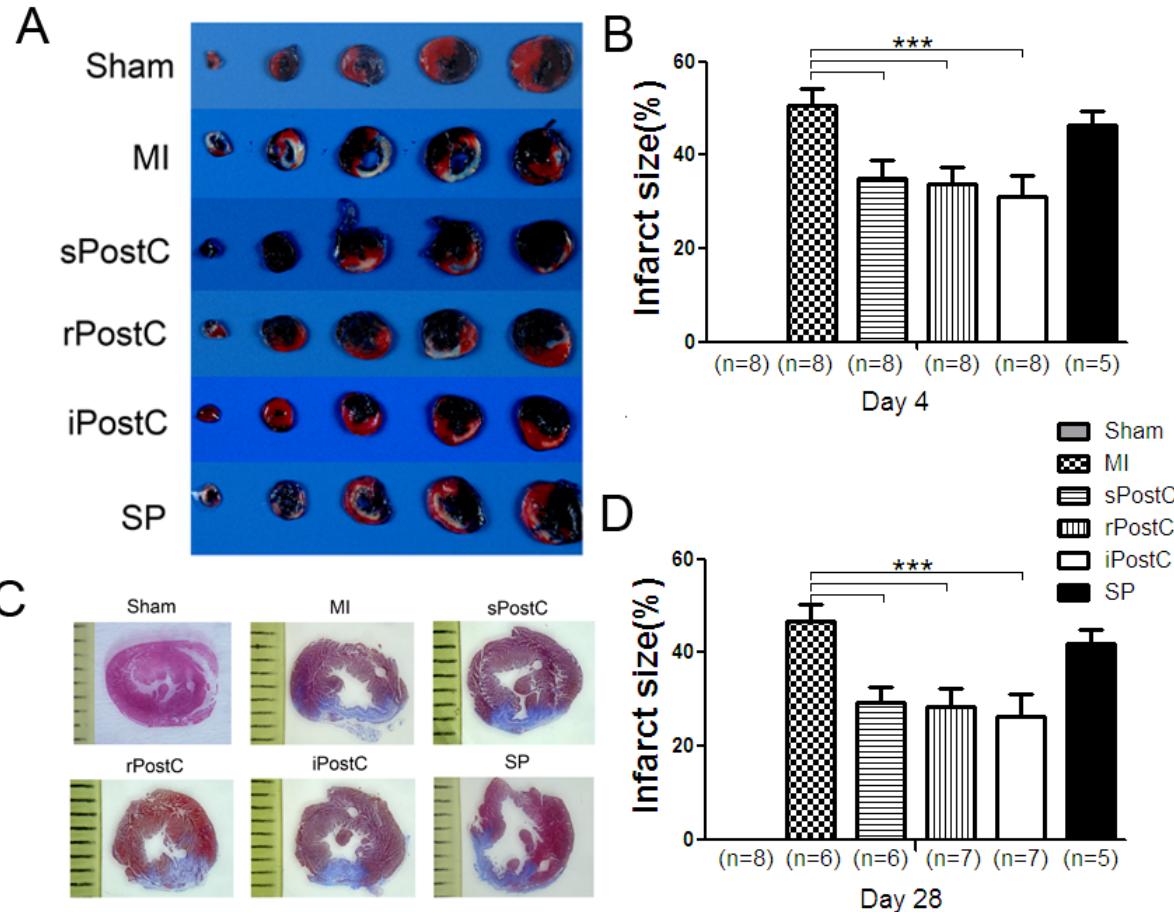


LAD Infarct 45' ischemia Reperfusion



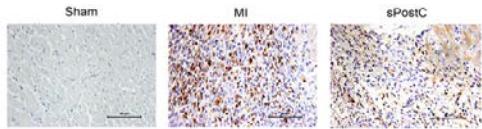


Post-MI Remodeling

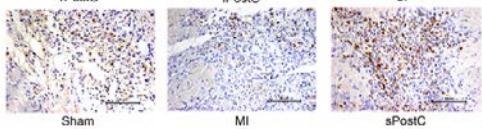




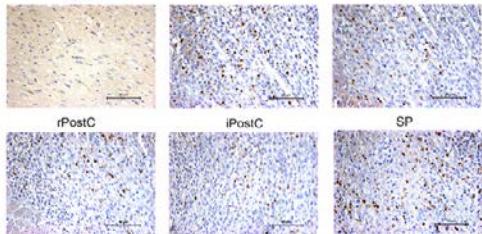
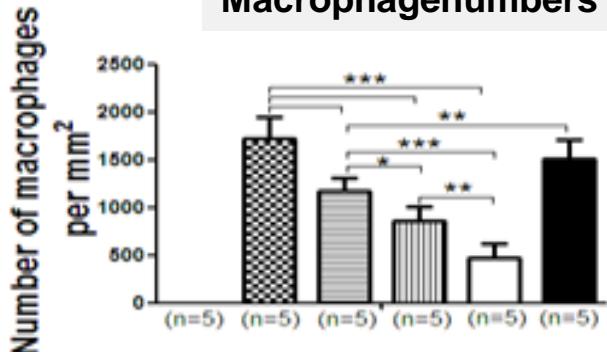
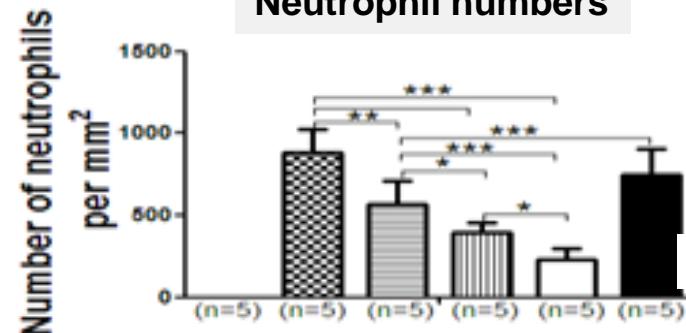
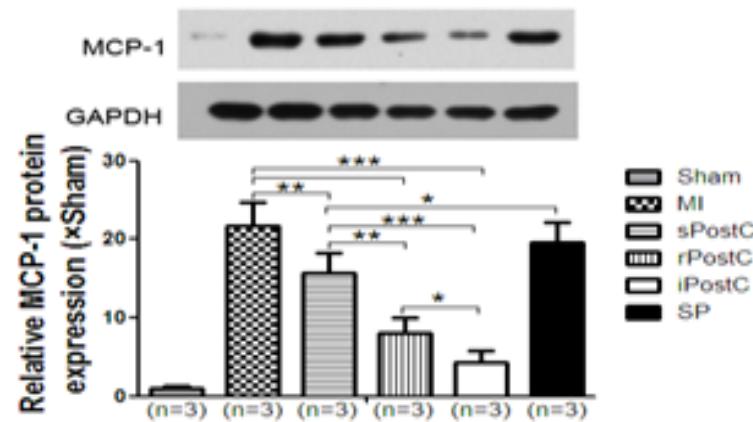
Post-MI Remodeling

**A**

Macrophages

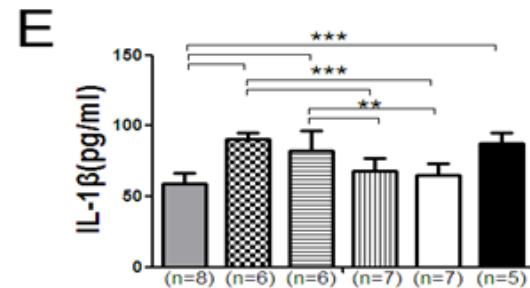
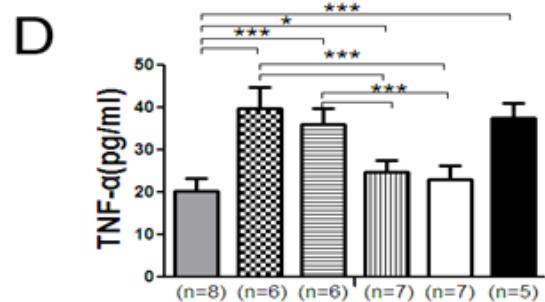
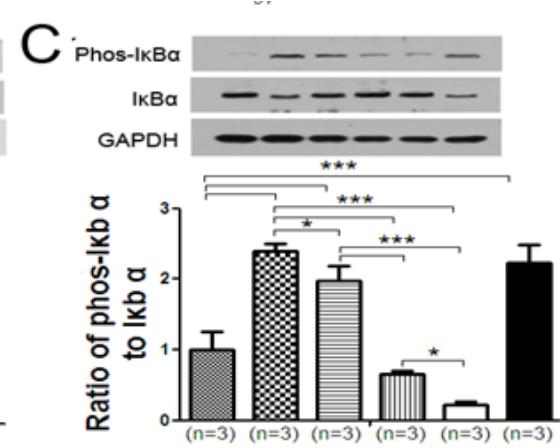
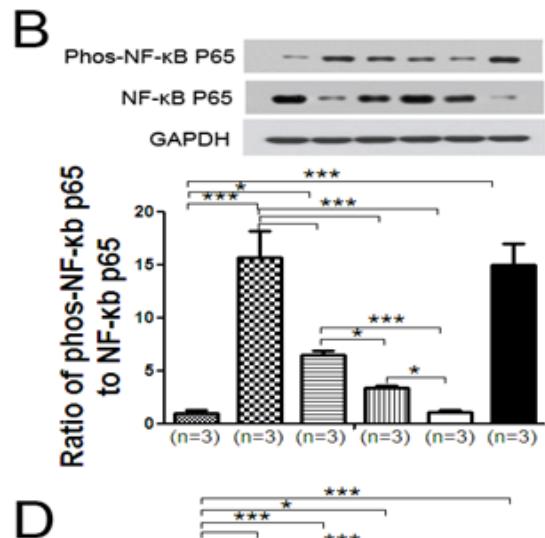
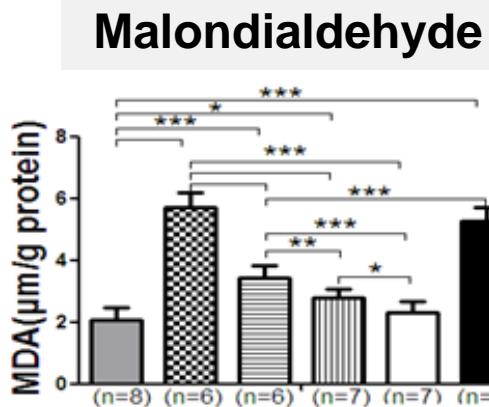
**B**

Neutrophils

**Macrophagenumbers****Neutrophil numbers****Monocyte Chemo-attractant protein**

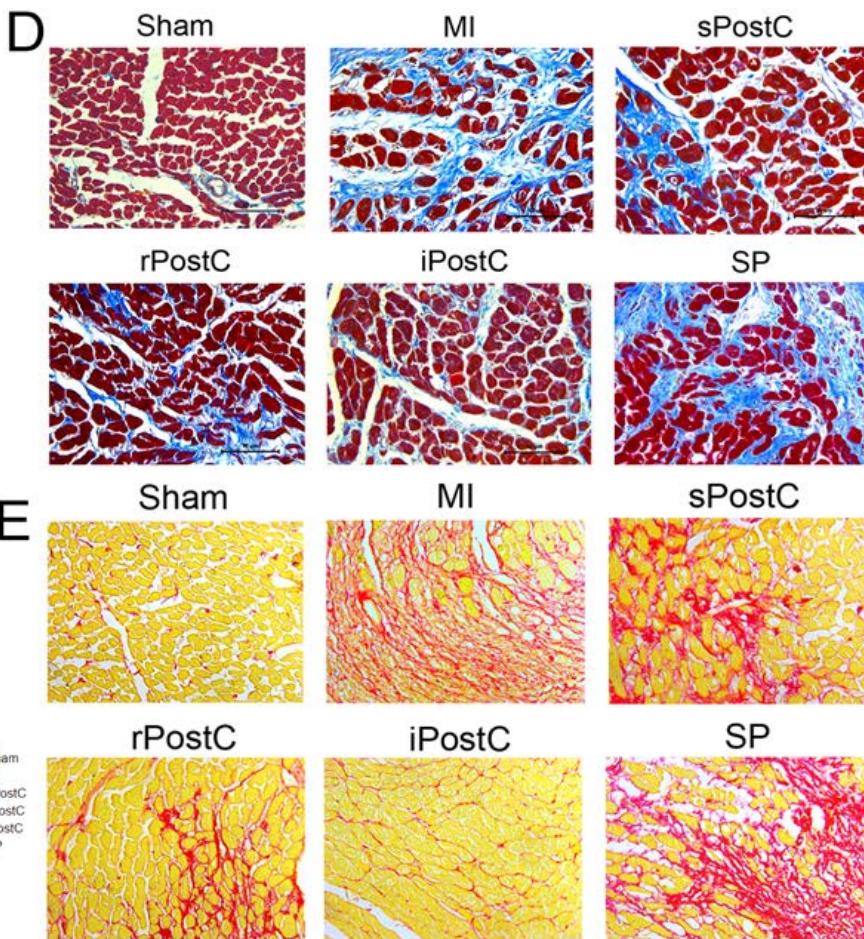
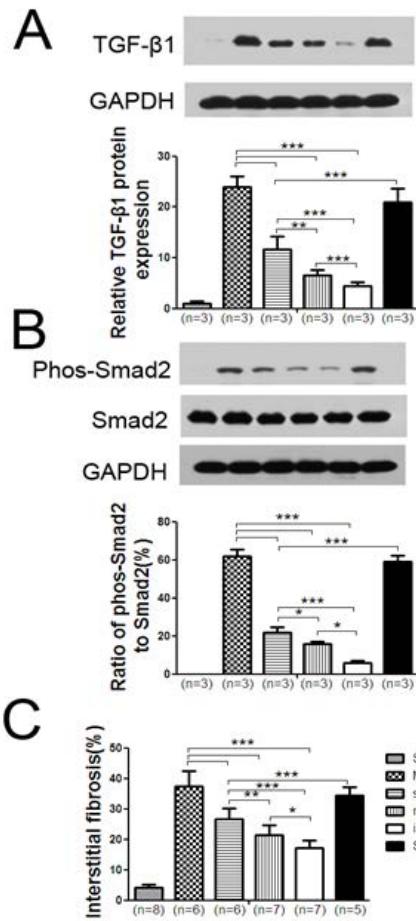


Post-MI Remodeling: Proinflammatory signaling





Post-MI Remodeling: Fibrosis signaling

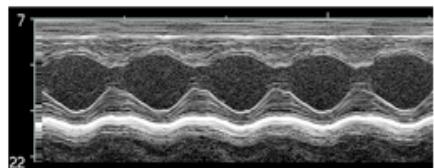


Mechanisms- Chronic RIC

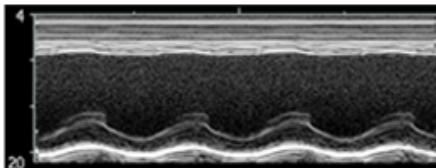
Fondation Leducq

A

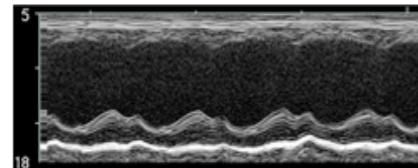
Sham



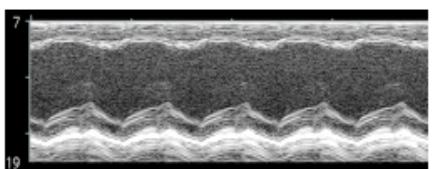
MI



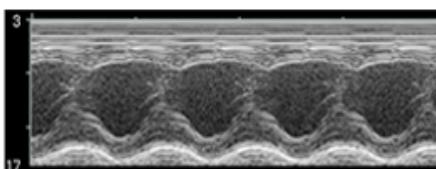
rIPerC



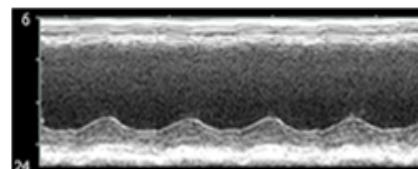
RIPC every 3 days



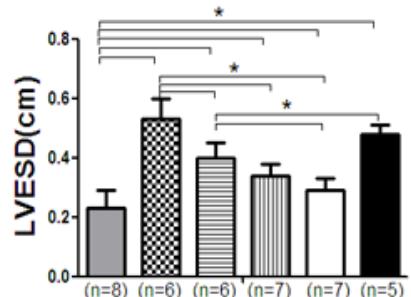
RIPC every day



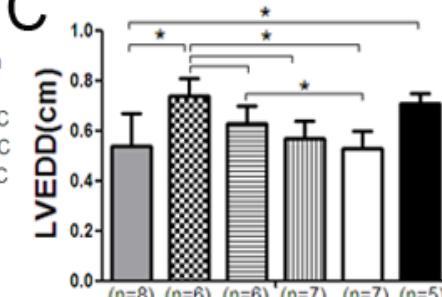
Pentobarbital Control



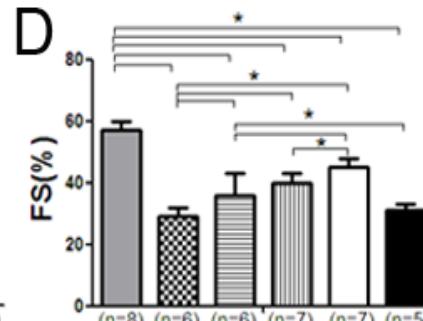
B



C



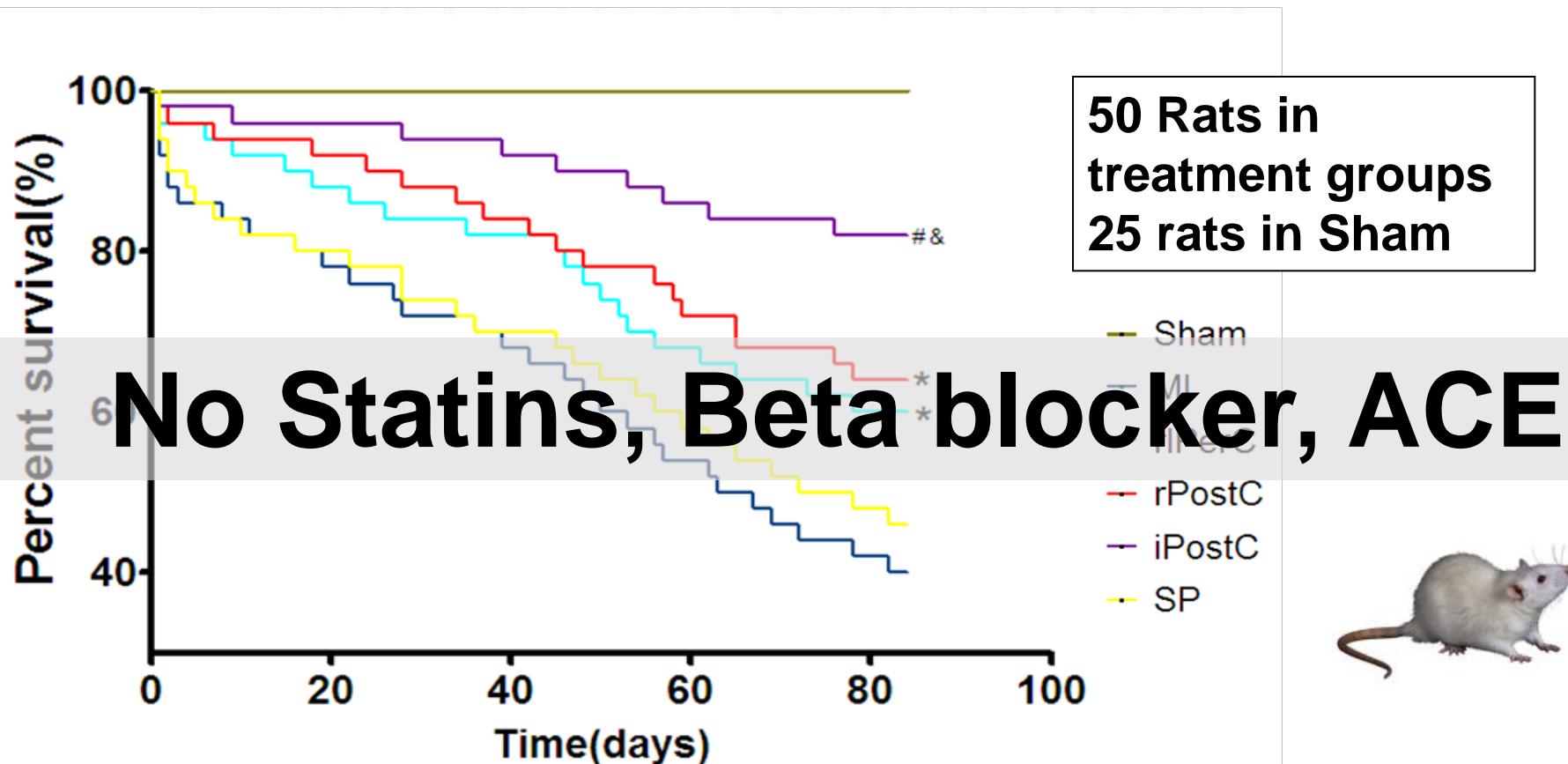
D



Mechanisms- Chronic RIC



Fondation Leducq



Neuroprotection

Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis

6

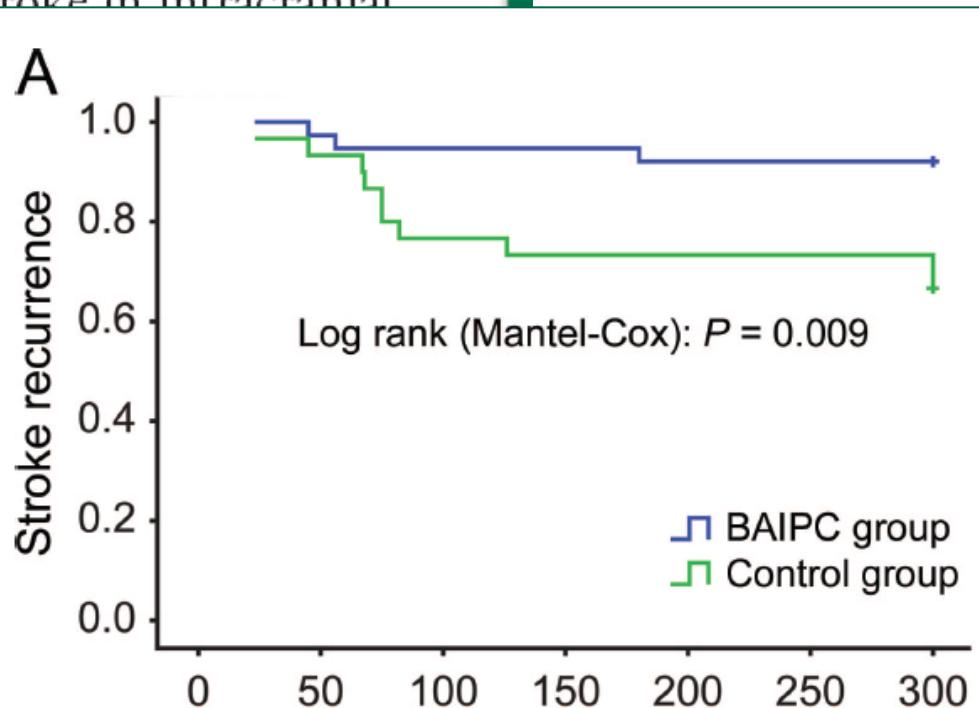
ABSTRACT

Objective: This study aims to evaluate preoperative arterial bypass (BAIPC) on stroke recurrence in patients with cranial arterial stenosis (IAS).

Methods: A total of 68 consecutive cases enrolled in this prospective and randomized study. Patients in the BAIPC group ($n = 34$) had upper limb ischemia followed by reperfusion over 300 consecutive days. Incidence of re-treatment in patients were compared with the control group.

Results: In the control group, incidence of r 26.7%, respectively. In the BAIPC group, 7.9% at 90 and 300 days ($p < 0.01$), respe Scale score 0-1) was also shortened by B and transcranial Doppler sonography, impr ($p < 0.01$).

Conclusion: This study provides a proof-of-concept that it is feasible to improve cerebral perfusion and reduce reperfusion injury in patients with stroke by using a noninvasive, nonpharmacological approach. The long-term safety and efficacy of this therapeutic approach will require further investigation.



Ran Meng, MD, PhD
Karam Asmaro, MS
Lu Meng, PhD
Yu Liu, MD
Chun Ma, MD
Chunjiang Xi, MD
Guoqing Li, MD
Canghong Ren, PhD
Yumin Luo, PhD
Feng Ling, MD
Jianping Jia, MD
Yang Hua, MD
Xiaoying Wang, PhD
Yuchuan Ding, MD,
PhD
Eng H. Lo, PhD
Xunming Ji, MD, PhD

Correspondence & reprint
requests to Dr. Ji:
jizm70@cmu.edu.cn

Neuroprotection

Autophagy 8:2, 222–235; February 2012; © 2012 Landes Bioscience

Stimulation of autophagy by rapamycin protects neurons from remote degeneration after acute focal brain damage

Maria Teresa Visconti,^{1,†} Marcello D'Amelio,^{1,2,†} Virve Cavallucci,¹ Laura Latini,¹ Elisa Bisicchia,^{1,3} Francesca Nazio,⁴ Francesca Fanelli,⁵ Mauro Maccarrone,^{1,3} Sandra Moreno,⁵ Francesco Cecconi^{1,4,‡} and Marco Molinari^{1,‡,*}

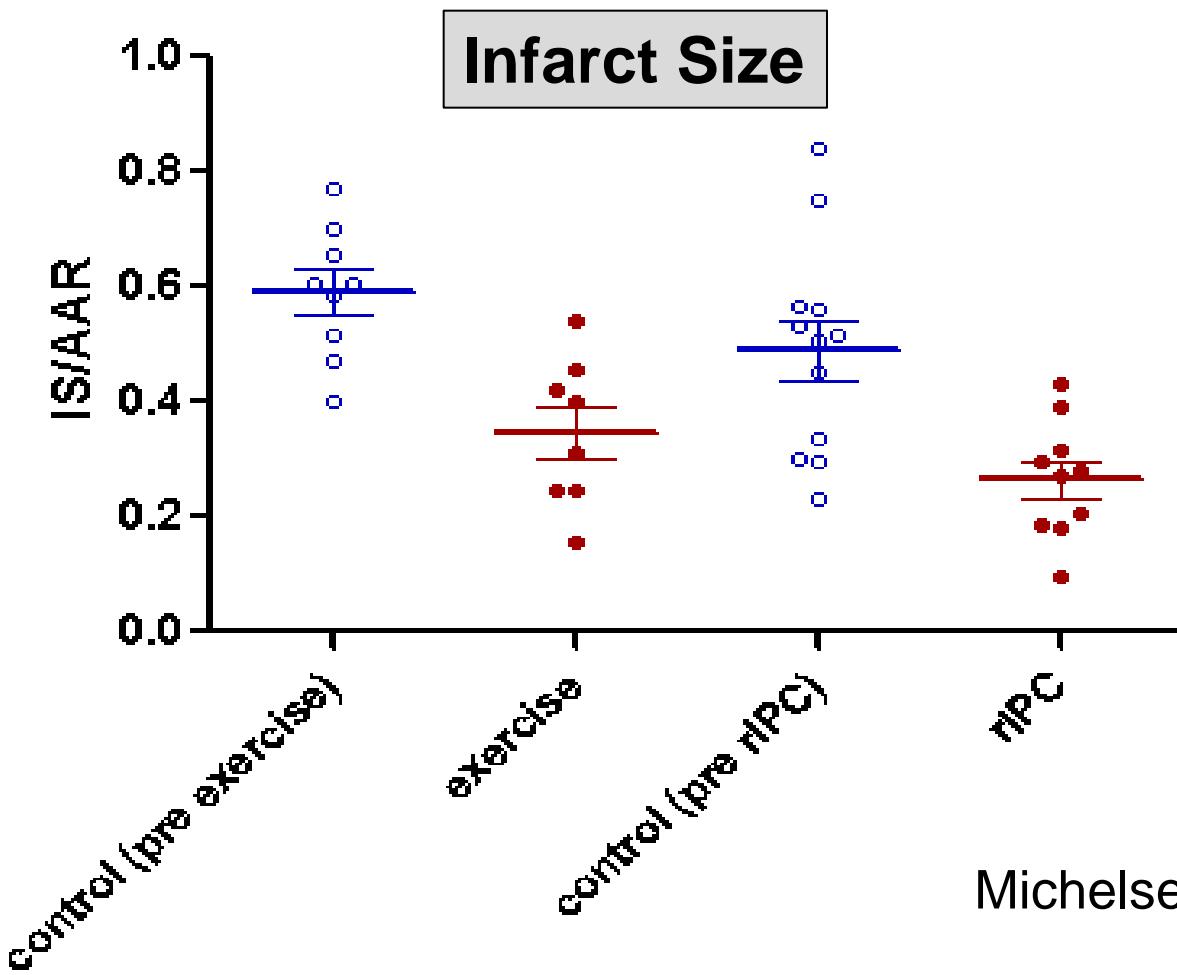
¹IRCCS S. Lucia Foundation; Rome, Italy; ²University Campus Bio-Medico; Rome, Italy; ³Department of Biomedical Sciences; University of Teramo; Teramo, Italy;

⁴Dulbecco Telethon Institute; Department of Biology; University of Rome ‘Tor Vergata’; Rome, Italy; ⁵Department of Biology-LIME; University “Roma Tre”; Rome, Italy

Exercise



Fondation Leducq



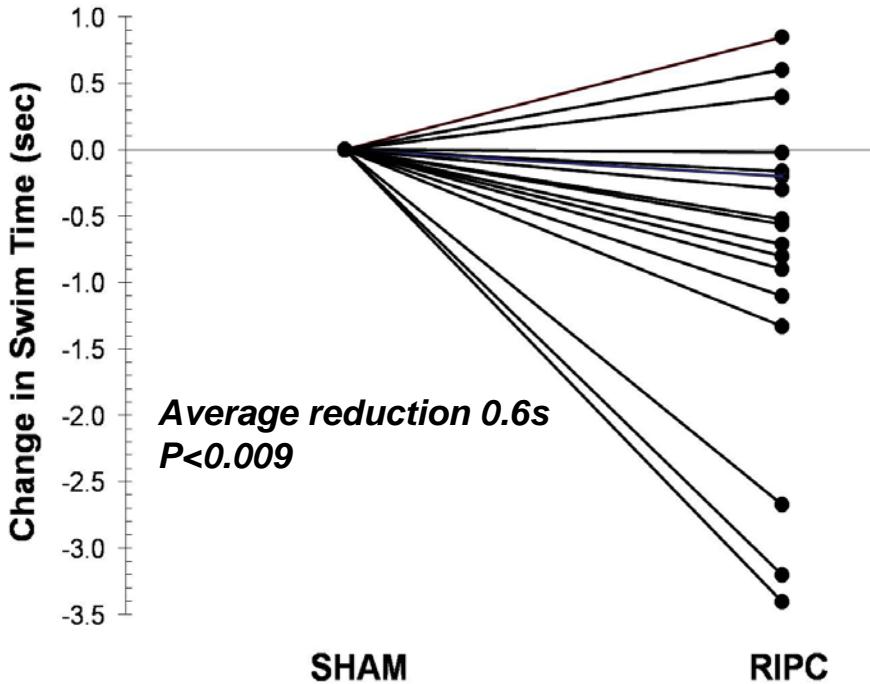
Michelsen. Bas Res Cardiol 2012

Applications: Exercise



Fondation Leducq

RIPC in Elite Swimmers



Jean-St Michel et al: MSSE 2011



Applications: Exercise



Fondation Leducq

Med Sci Sports Exerc 2012 Nov;44(11):2084-9..

Effect of Ischemic Preconditioning on Lactate Accumulation and Running Performance

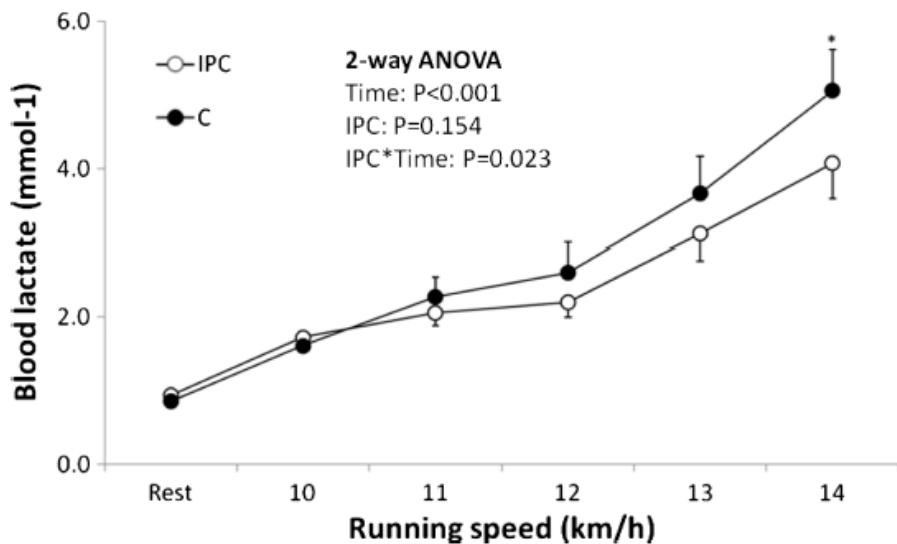


FIGURE 1—Blood lactate levels at rest at all five submaximal stages during the incremental running test with exercise being preceded by IPC (solid circles) or C (open circles). Error bars represent standard error (SE). *Post hoc significantly different between C and IPC.

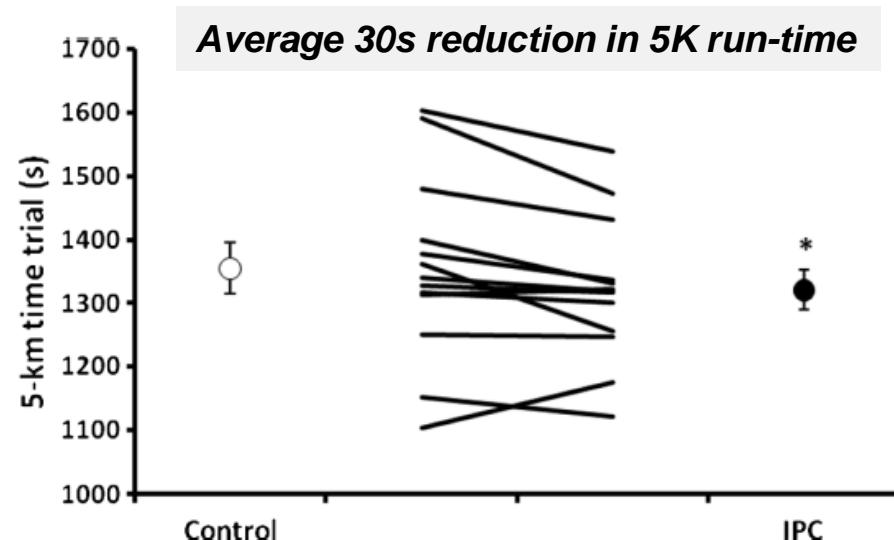
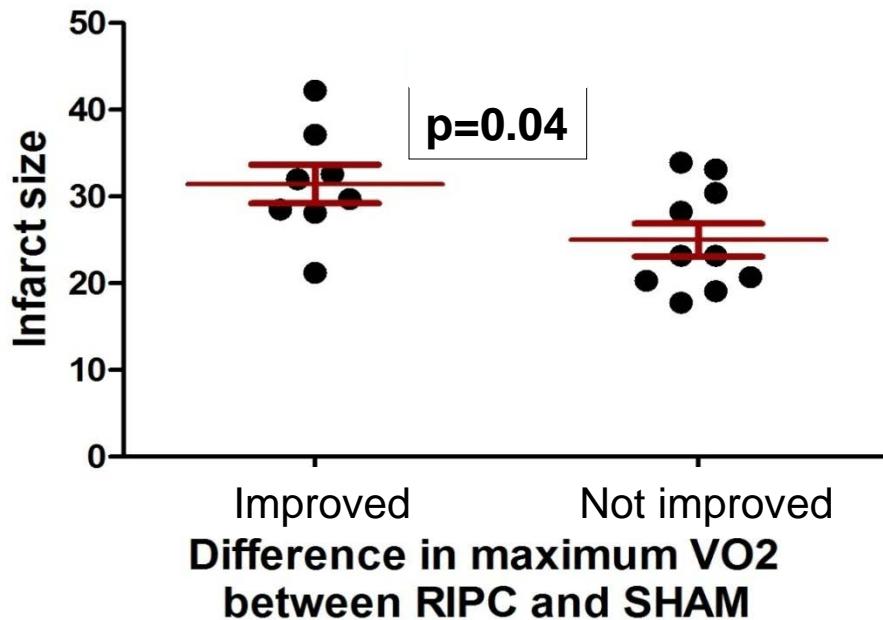
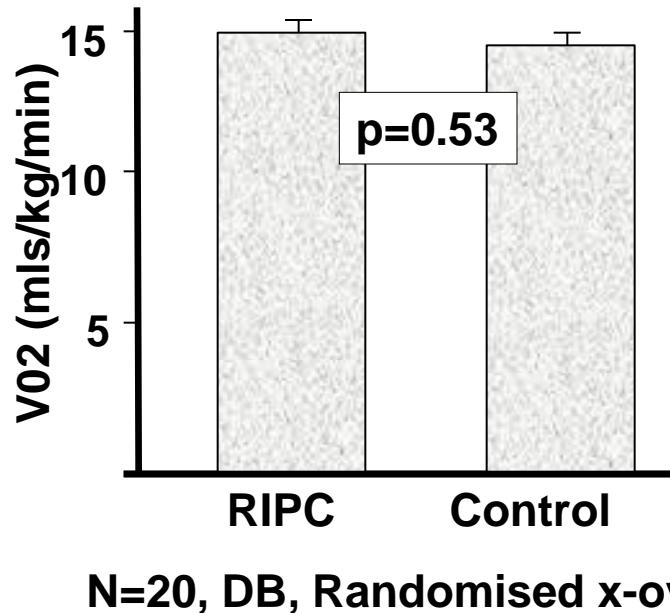


FIGURE 2—Individual and mean (SE) data on 5-km time trial performance after IPC and C in healthy young men ($n = 13$). *Denotes a significant treatment effect of IPC ($P = 0.027$).

Heart Failure: Already preconditioned?

RIPC in Adult Heart Failure



MacDonald et al. In press 2014

Conclusions

- Remote conditioning has acute, delayed and ‘chronic’ effects
- Rapid translation into proof-of-principle studies
- Definitive RCT’s awaited in major clinical areas
- Emerging potential areas of application