Remote ischemic conditioning and physical training - Modifying risk in ischemic heart disease

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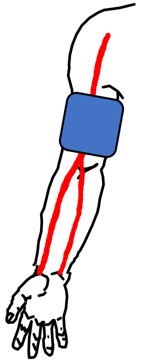
Concept of remote preconditioning

Intraorgan remote

Occlusion of CX
Infarct size in LAD

Przyklenk K et al. *Circulation* 1993;87:893-9

Interorgan remote

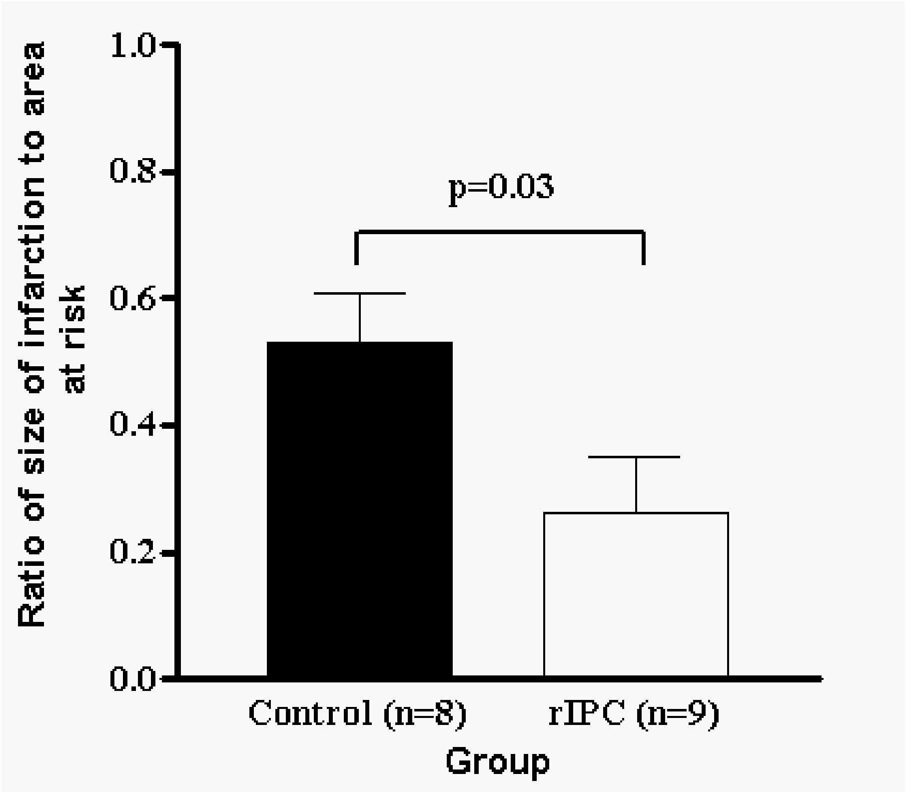


Four cycles of 5 minutes of limb ischemia induced by blood pressure cuff inflation (200 mm Hg)

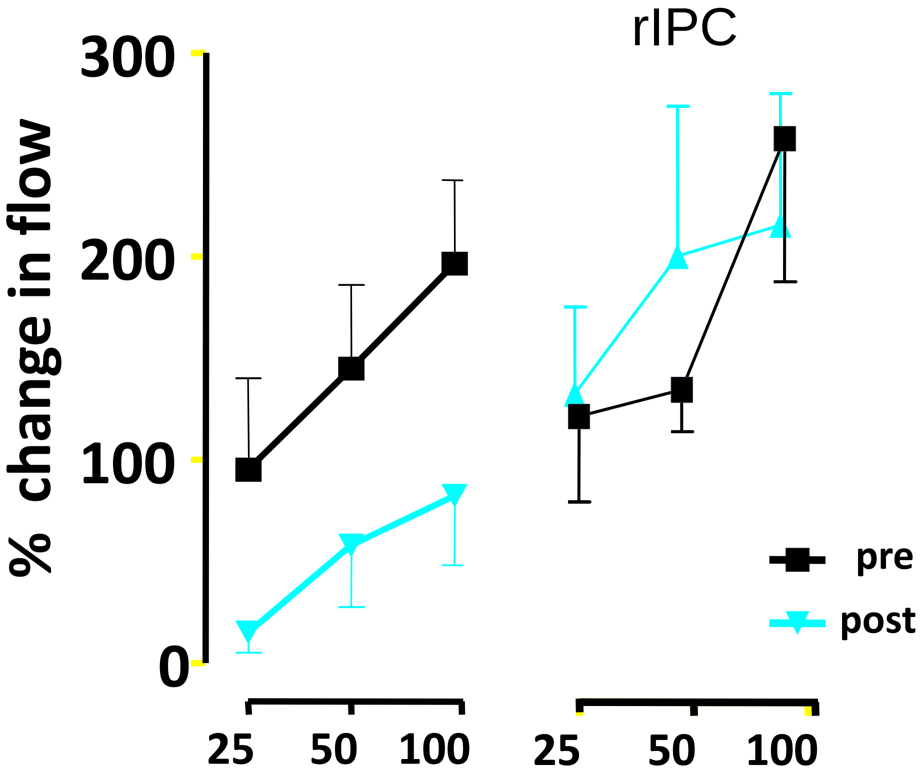
Birnbaum Y et al. *Circulation* 1997;96:1641-6
Kharbanda R et al. *Circulation* 2002;106:2881-3

Activation of endogenous cardioprotection: Remote Preconditioning by limb ischaemia

Animal Infarction model



Human forearm model



Kharbanda et al, Circulation, 2002;106:2881-3

Remote ischemic conditioning

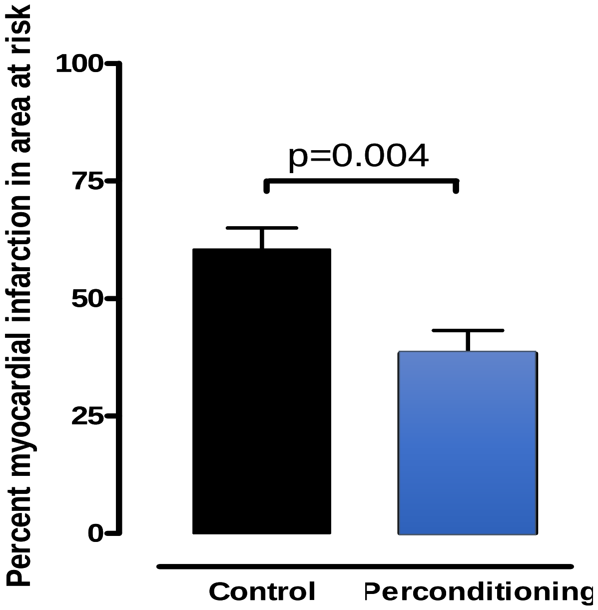
- Coming from IPC
- The concept
- Mimicking claudication?
- The warm-up phenomenon

5 min. Inflation	5 min. Deflation	5 min. Inflation	5 min. Deflation	5 min. Inflation	5 min. Deflation	5 min. Inflation

Inflates to 200 mm Hg

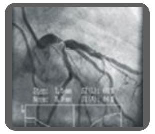
Remote conditioning

Experimental

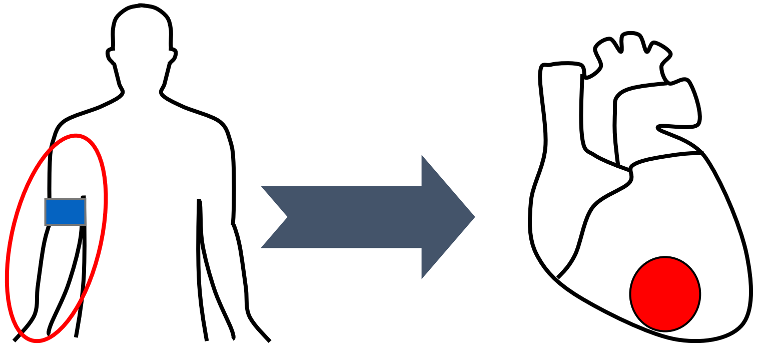


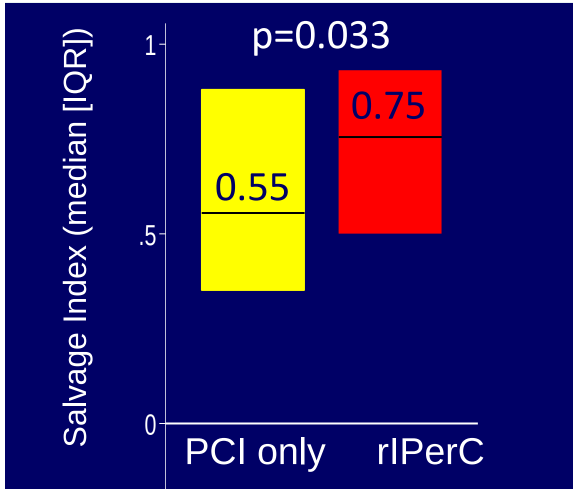
Schmidt MR et al. Am J Physiol Heart Circ Physiol 2007;292:H1883-90.

Clinical



Remote perconditioning during ambulance transport in patients with acute myocardial infarction





Bøtker et al. *Lancet* 2010; 373: 727-34

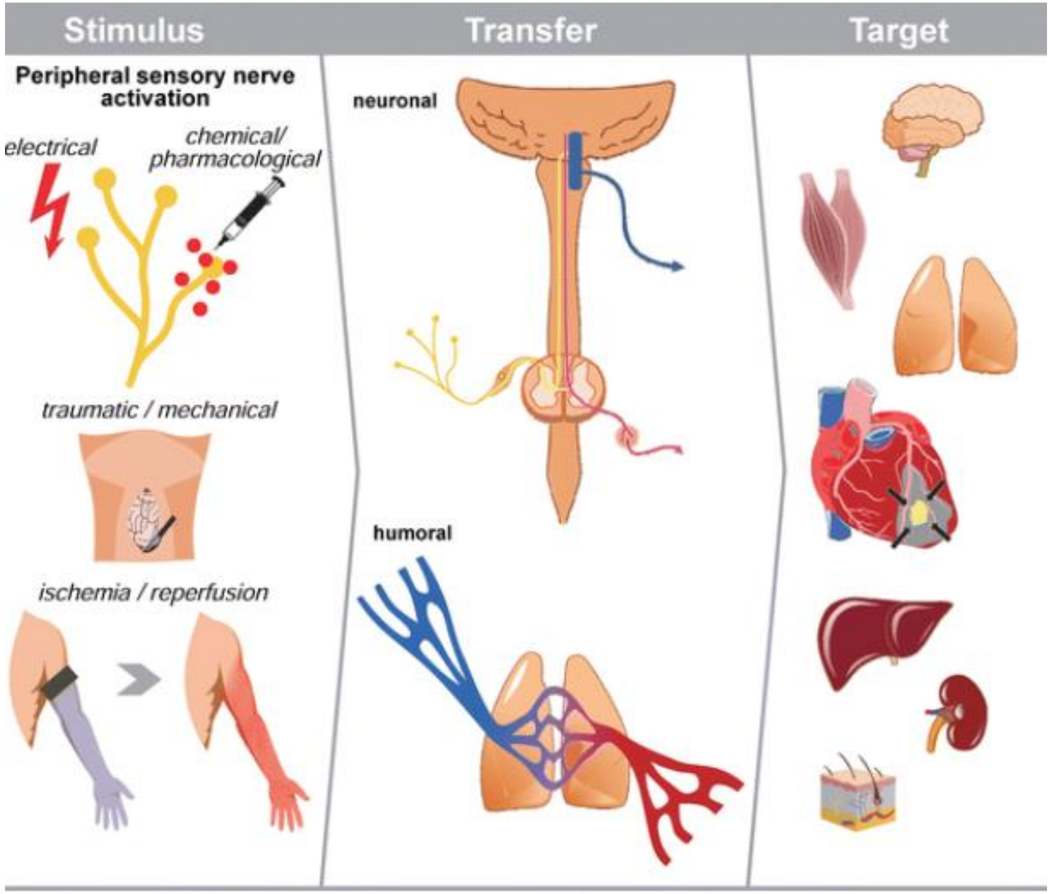
Efficacy of RIC in humans

Study	No of patients (control/RIC)	RIC regimen	Endpoint	Outcome
Bøtker et al. 2010	69/73	Upper limb 4 cycles I/R (5/5 min)	Salvage index (SPECT)	20% increase in salvage index
Munk et al. 2010	110/108	Upper limb 4 cycles I/R (5/5 min)	LVEF at 30 days	5% increase in LVEF in anterior infarcts
Rentoukas et al. 2010	30/33	Upper limb 3 cycles I/R (5/5 min)	ST-segment resolution	20% increase in patients achieving full ST-segment resolution
Crimi et al. 2013	50/50	Lower limb 3 cycles I/R (5/5 min)	CK-MB (AUC 72 h after PCI)	20% reduction of CK-MB release
Prunier et al. 2014	17/18	Upper limb 4 cycles I/R (5/5 min)	CK-MB (AUC 72 h after PCI)	31% reduction of CK-MB release
Sloth et al. 2014	167/166	Upper limb 4 cycles I/R (5/5 min)	MACCE at 4 yr	12% reduction in MACCE
Yamanaka et al. 2014	62/63	Upper limb 3 cycles I/R (5/5 min)	Acute kidney injury (rise in creatinine)	72 % reduction in acute kidney injury
Yellon et al. 2015	258/261	Upper limb 4 cycles I/R (5/5 min)	TnT (AUC 24 h after PCI)	17% reduction of TnT release
Eitel et al. 2015	232/232/232	Upper limb 3 cycles I7T (5/5 min) + local post CON	Salvage index (MRI)	23 % increase in salvage index
White et al. 2015	40/43	Upper limb 4 cycles I/R (5/5 min)	Myocardial edema (MRI)	27 % reduction in myocardial edema
Olafiranye et al. 2016	92/127	Upper limb 4 cycles I/R (5/5 min)	Acute kidney injury (rise in creatinine)	53 % reduction in acute kidney injury
Verouhis et al 2016	46/47	Lower limb 4+ cycles I/R (5/5 min) Per + post	Salvage index (MRI)	No effect
Lotfollahi et al. 2016	29/32	Upper limb 3 cycles I/R (5/5 min)	Oxidative stress	100 % increase in total anti-oxidative capacity

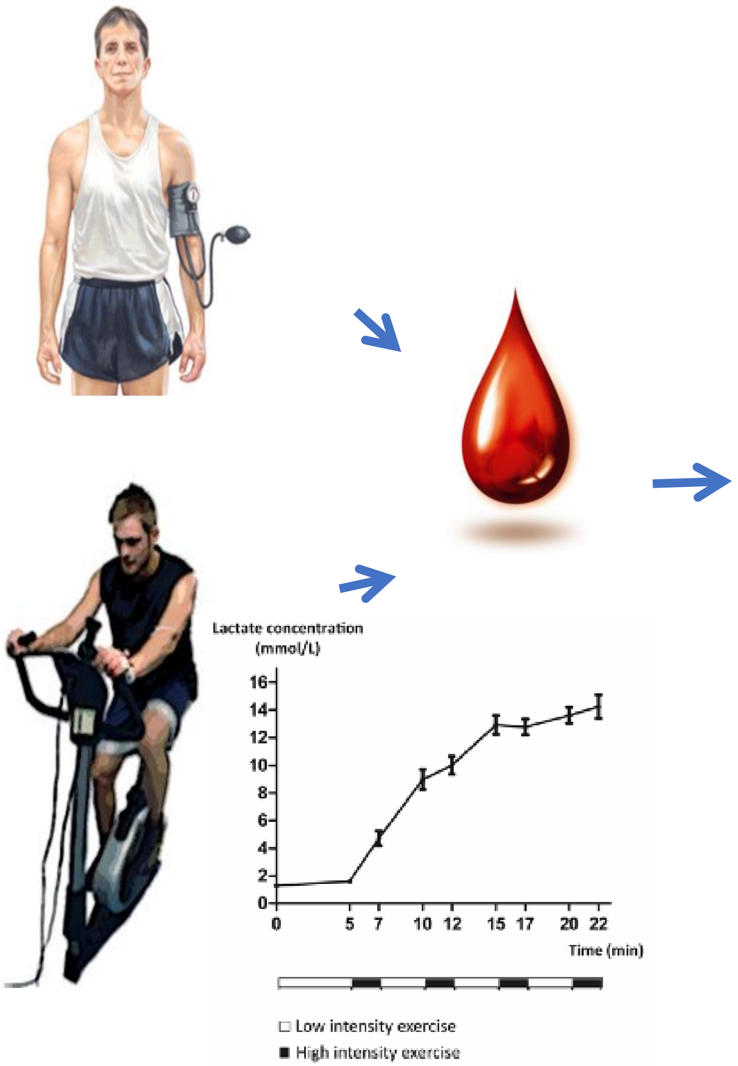
Schmidt, Rasmussen, Bøtker. J Cardiovasc Pharmacol Ther 2017, 22:302-309

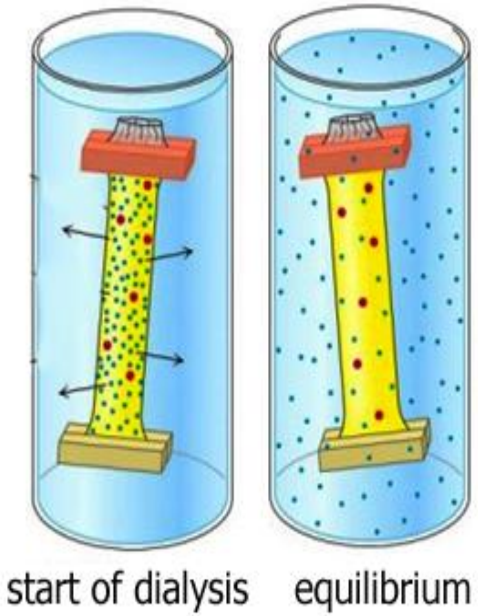
How does RIC work?

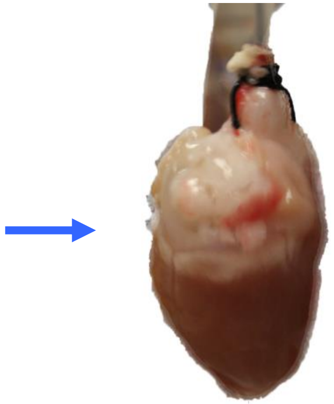
- Multiple triggers
- Parallel pathways
- Dynamic course of protection
- Systemic effects
- Trigger, mediator, effector – Too simplified?



Dialysate as a bioassay for RIC: Human to rabbit transfer



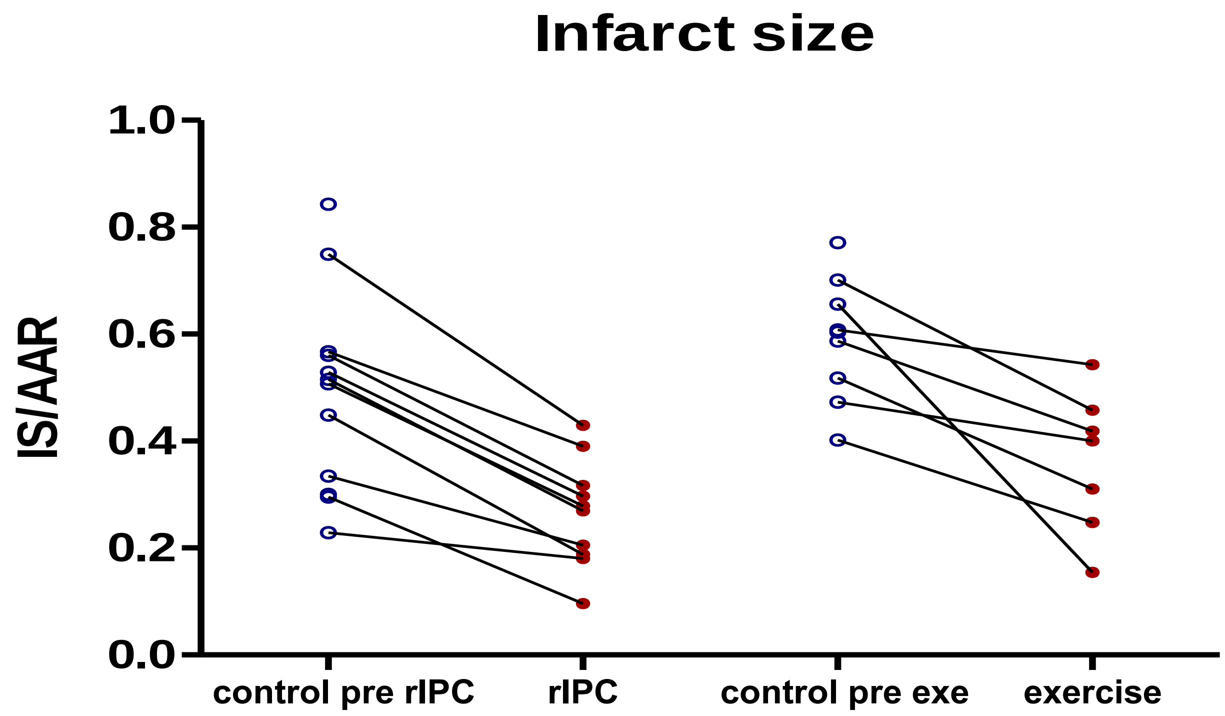




Shimizu et al. Clin Sci 2009;117:191-200
Michelsen et al. Basic Res Cardiol. 2012;107:260

Cardioprotection with RIC and exercise

Human to rabbit transfer



mean ± SEM:	49 % ± 5 %	27 % ± 3 %	59 % ± 4%	35 % ± 5

Michelsen et al. Basic Res Cardiol. 2012;107:260

Mediating substance: endogenous opioids?

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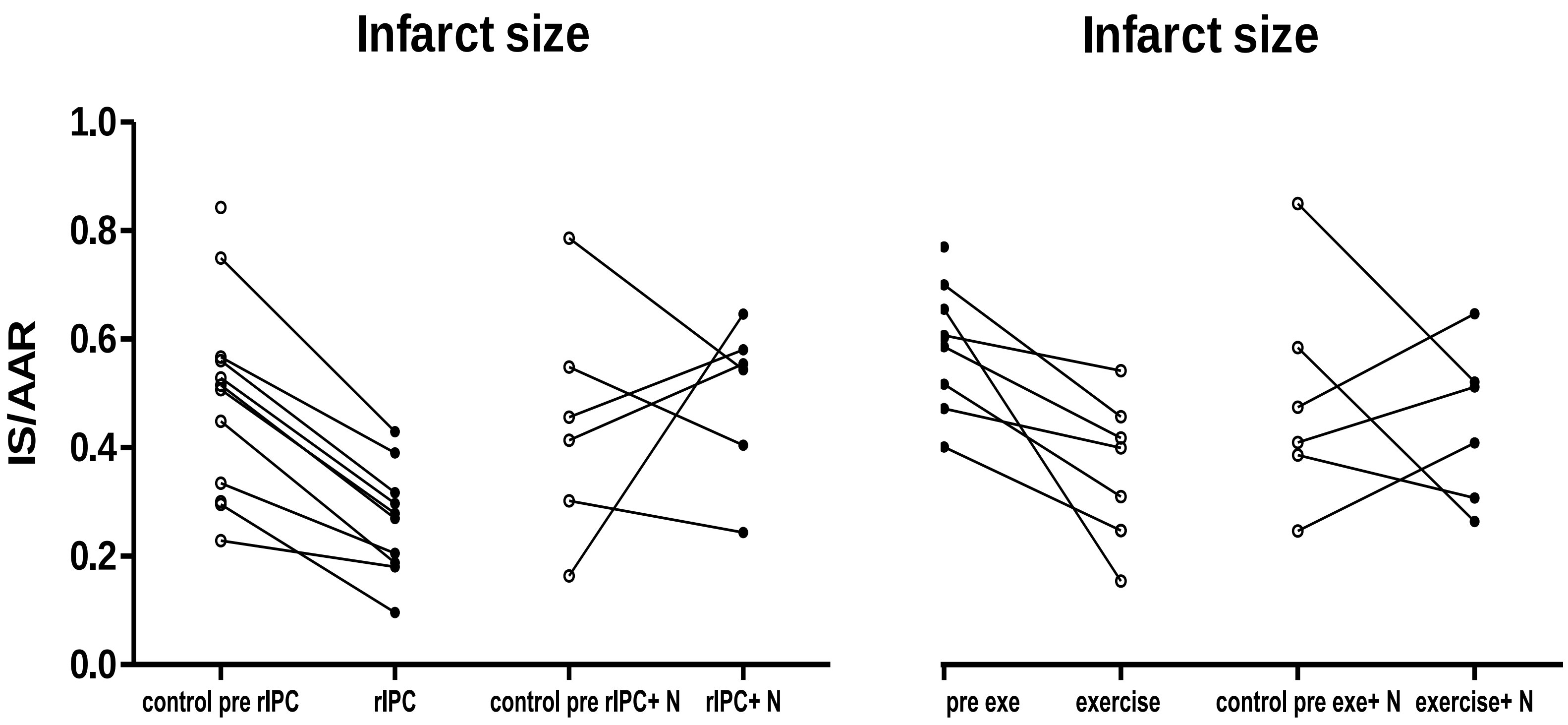
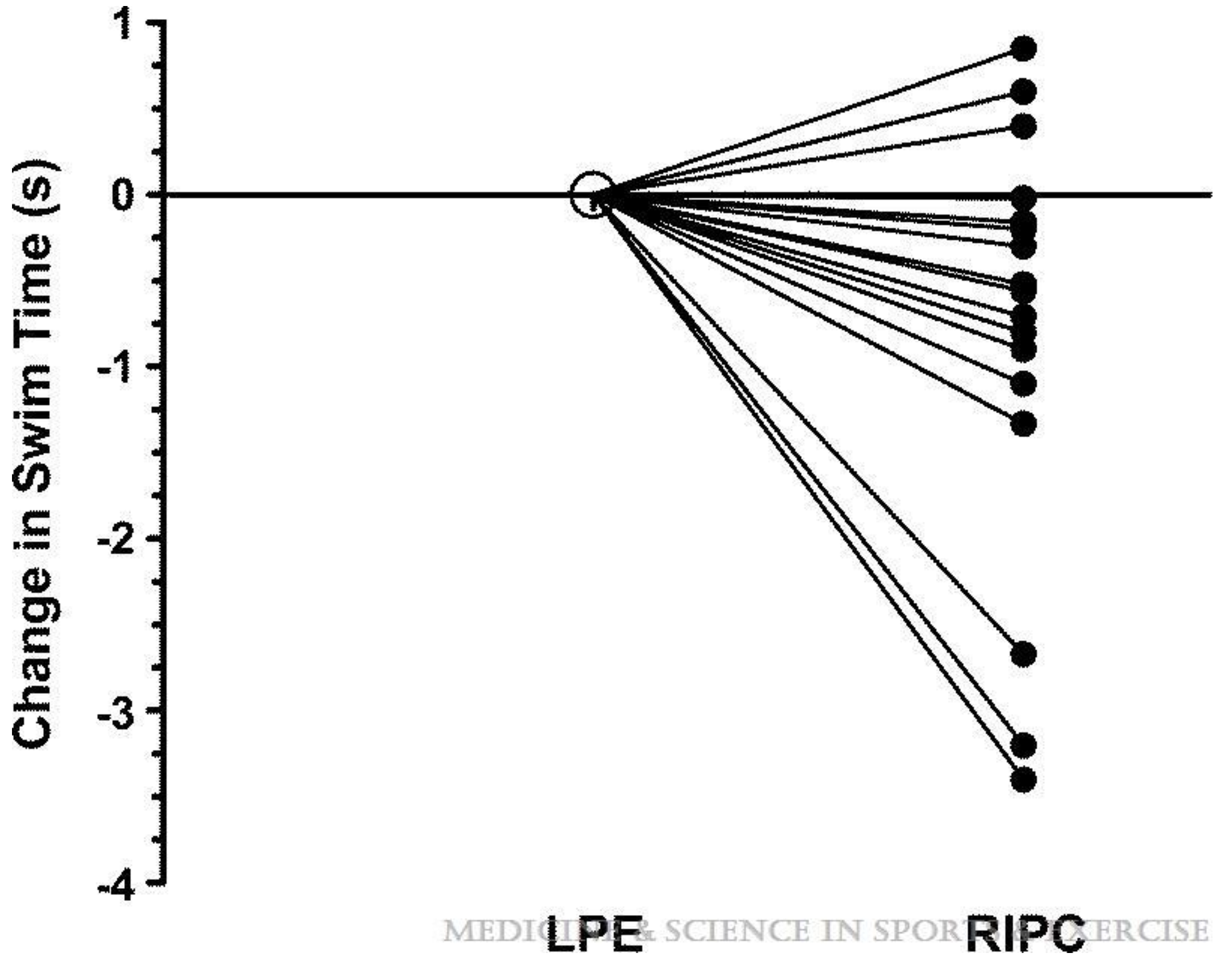
Human to rabbit transfer



Michelsen et al. Basic Res Cardiol. 2012;107:260

Can biological performance and resilience be enhanced or extended?



RIC improves maximal performance in highly trained athletes

Jean-St-Michel et al. Med Sci Sports Exerc. 2011; 43:1280-1286

Effect of RIC on aerobic/anaerobic performance

<table>
<tr><th>Sports Setting</th><th>Design</th><th>Algorithm</th><th>Outcomes</th></tr>
<tr><td>Aerobic:
Elite swimmers, 100 m freestyle (1)</td><td>40 athletes, crossover design</td><td>4 x 5/5 mins</td><td>RIPC improves swim performance by 0.6 seconds per 100 metres swim distance</td></tr>
<tr><td colspan="4">Level of improvement approximately equal to 18 months of training.</td></tr>
<tr><td>Aerobic:
Cycling (2)</td><td>15 athletes, crossover design</td><td>3 x 5/5 mins</td><td>RIC improves cycling performance. Oxygen consumption increases 3%, power output increased 1.6%.</td></tr>
<tr><td colspan="4">Oxygen consumption improvement comparable to ~1 month of altitude training.</td></tr>
<tr><td>Aerobic:
Running, regular (non-elite) exercisers (3)</td><td>13 volunteers cross-over trial</td><td>3 x 5/5 mins</td><td>30 second reduction in 5K time in regular, non-elite, exercisers</td></tr>
<tr><td>Aerobic/Submaximal performance:
Cycling (4)</td><td>12 athletes cross-over trial</td><td>3 x 5/5 mins</td><td>RIC did not improve submaximal performance</td></tr>
<tr><td colspan="4">RIC would not be expected to have an effect on submaximal performance. At maximal endurance, performance is limited by the balance of substrate delivery and demand/tolerability of lack of delivery, and RIC modifies this balance.</td></tr>
<tr><td>Anaerobic: Land-based sprinting/ Team sport athletes (5)</td><td>25 athletes cross-over trial</td><td>3 x 5/5 mins</td><td>No significant effects of the preconditioning treatment were observed on sprint speed ($P < .05$) at any of the split timings.</td></tr>
<tr><td colspan="4">This result is not surprising as land-based sprint as there would be no effect/impact of ischemia on performance due to the short duration of activity.</td></tr>
</table>

CONDI-HF
Effect on RIC in chronic heart failure

28 days of daily RIC

Patients with CHF (n=22)	Baseline	Follow-up	CI	p-value
LV ejection fraction (%)	44 ± 9.7	44 ± 9.2	-0.89 to 0.55	p=0.63
LV end-diastolic volume (ml)	223 ± 61.1	220 ± 63.4	-10.01 to 4.09	p=0.39
Stroke volume (ml)	94 ± 22.8	93 ± 21.7	-5.39 to 1.96	p=0.34
GLS - strain rate (%)	-8.9 ± 2.2	-9.5 ± 2.5	-1.18 to 0.13	p=0.11
Systolic blood pressure (mmHg)	130 ± 14.2	124 ± 16.8	-10.03 to -2.67	p=0.0018
Control subjects (n=21)				
LV ejection fraction (%)	71 ± 5.2	71 ± 5.3	-0.15 to 0.44	p=0.32
LV end-diastolic volume (ml)	148 ± 32.9	147± 32.9	-3.40 to 1.59	p=0.46
Stroke volume (ml)	104 ± 23.3	104 ± 24.0	-2.00 to 1.39	p=0.71
GLS - strain rate (%)	-14.1 ± 1.5	-14.6 ± 1.4	-1.07 to 0.24	p=0.20
Systolic blood pressure (mmHg)	145 ± 15.2	140 ± 13.7	-9.30 to 0.73	p=0.09

No effect of RIC on LV-EF (primary endpoint)
Blood pressure reduced

Pryds et al. Basic Res Cardiol. 2017;112:67

Exercise capacity and muscle strength

Patients with CIHF	BASELINE	Follow-up	CI	P-value
Peak cardiopulmonary exercise capacity:				
- Workload (W/kg)	1.6 ± 0.31	1.6 ± 0.33	-0.02 to 0.08	p=0.26
- Oxygen uptake (ml/kg/min)	19.9	20.1		p=0.59
Leg Extensor Power Rig (W/kg)	2.3 ± 0.8	2.5 ± 0.8	0.02 to 0.21	p=0.02
Control subjects				
Peak cardiopulmonary exercise capacity:				
- Workload (W/kg)	2.3 ± 0.5	2.2 ± 0.5	- 0.07 to 0.04	p=0.61
- Oxygen uptake (ml/kg/min)	28.2 ± 5.8	27.1 ± 5.4	-2.34 to 0.22	P=0.10
Leg Extensor Power Rig (W/kg)	2.4 ± 0.8	2.6 ± 0.8	0.04 to 0.38	p=0.02

No effect on CPX
Skeletal muscle strength increased

Pryds et al. Basic Res Cardiol. 2017;112:67

NTPro-BNP and subgroup

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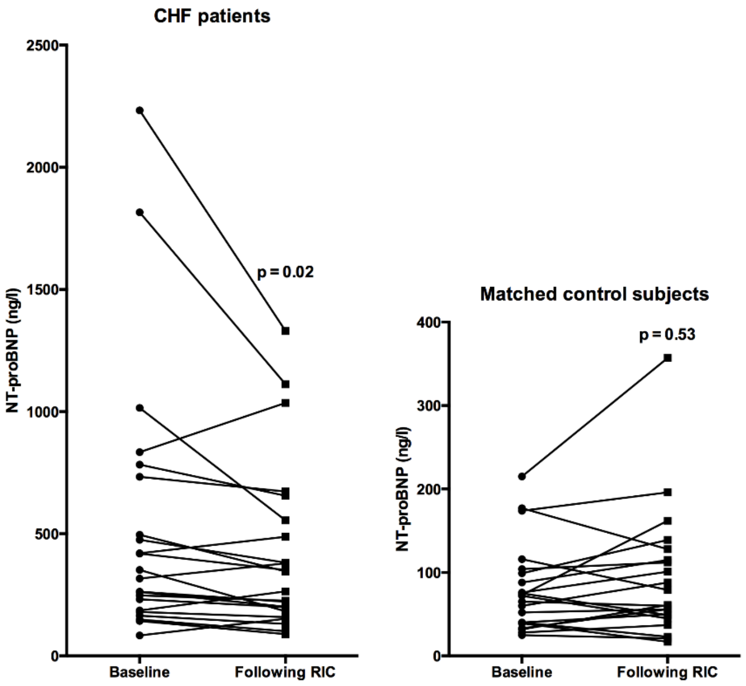


	Baseline	Follow-up	CI	p-value
Patients with CHF and NT-proBNP > 350 ng/l (n=11)				
LVEF (%)	43 ± 10.8	43 ± 10.6	-0.41 to 0.55	p=0.75
CO (ml/min)	4.6 ± 1.1	4.2 ± 1.2	-0.76 to 0.04	p=0.075
GLS - strain rate (%)	-8.8 ± 2.7	-9.8 ± 2.6	-2.09 to 0.03	p=0.055
Systolic BT (mmHg)	132 ± 11.6	126 ± 14.9	-12.35 to -1.01	p=0.025
Diastolic BT (mmHg)	78 ± 8.2	74 ± 7.8	-7.71 to 1.07	p=0.12
MAP (mmHg)	96 ± 7.8	92 ± 9.5	-8.70 to -0.18	p=0.04
NT-proBNP (ng/l)	724	556	-	p=0.01

- NT-proBNP reduction
- BP decrease
- Borderline increase in myocardial contractility

Pryds et al. Basic Res Cardiol. 2017;112:67

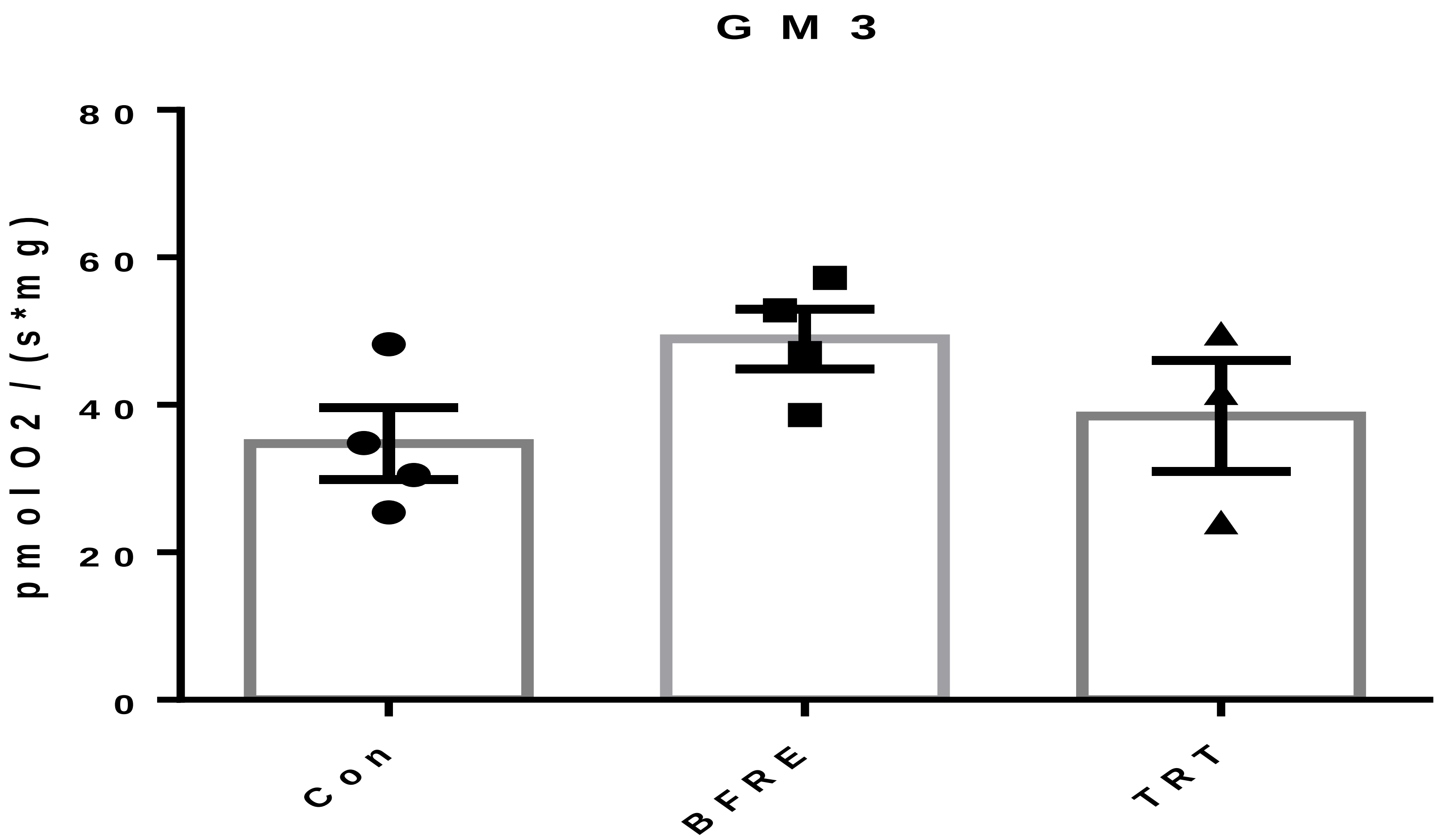
Human experimental models

Remote Ischemic Conditioning (RIC): upper arm ischemia achieved by intermittent inflation of a blood pressure cuff interspaced by reperfusion between inflations. The procedure will be performed **using the AutoRIC™** (CellAegis Devices Inc., Toronto, Ontario, Canada).

Bloodflow-restricted Resistance Exercise (BFRE): **A pneumatic cuff** is placed at the proximal part of the thighs (bilateral). The cuff's are inflated to 50% puls-elimination-pressure (PEP) and **connected to an electronic system (tourniquet), which regulate the cuff pressure during motion**. After a brief warm-up the participants perform **4-5 sets of bilateral knee extensions at 30% of 1RM until concentric contraction failure.** The sets are intercepted by 30 seconds of rest (during rest the cuff's are still inflated).

Traditional Resistance Exercise (TRT) – included to allow BFRE versus TRT comparison: Conventional moderate to heavy intensive resistance exercise (i.e., **3-4 sets of 10-15 repetitions in a isolated knee extensor apparatus, with a load equalling 15RM and inter-set recovery of 3 minutes**).

Influence of training and BFRE on mitochondrial respiration



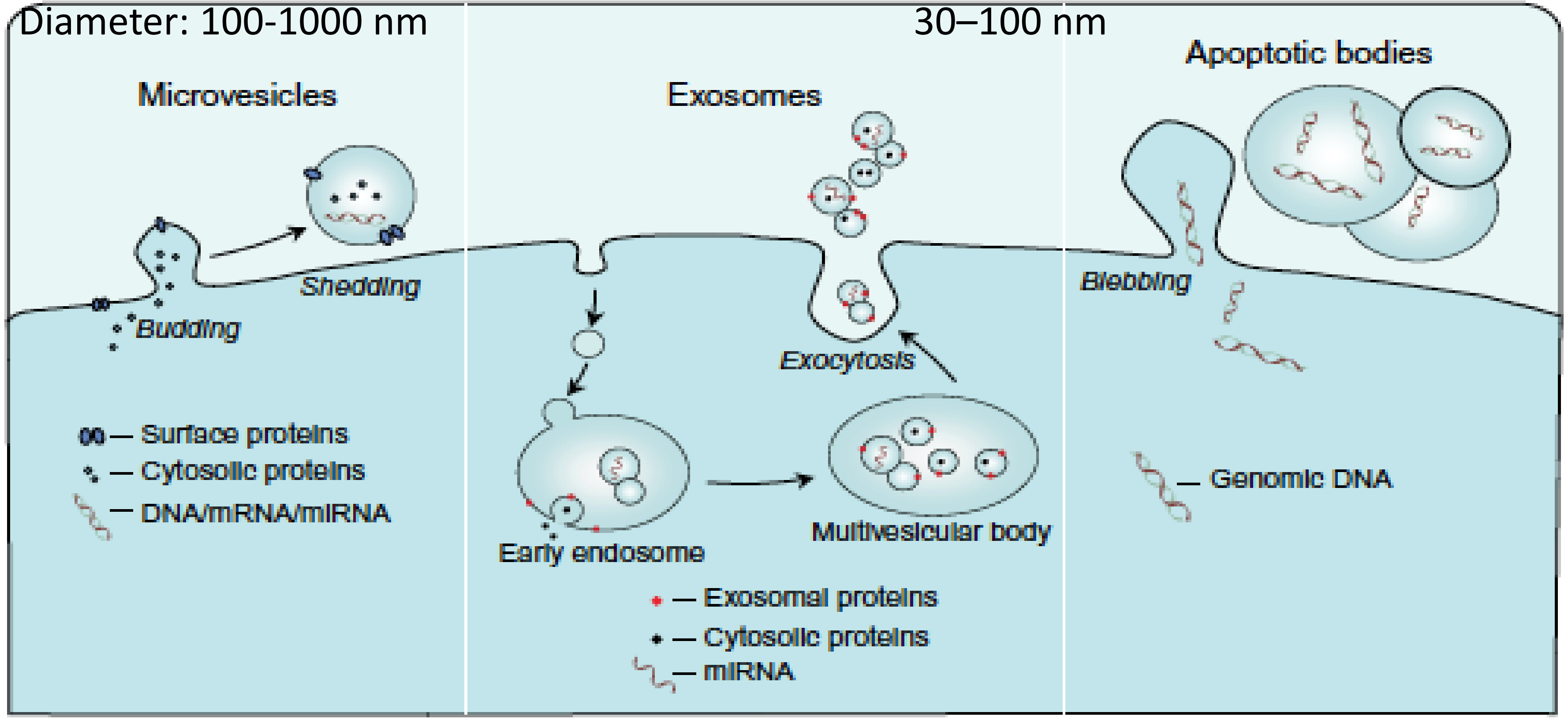
Interorgan communication and transfer

- Exosomes, microvesicles and apoptotic bodies are membrane-bound structures secreted by a wide range of mammalian cell types via distinct mechanisms.
- Their content of multiple compounds including proteins, mRNAs and microRNAs, renders EV ideal conveyors of inter-organ communication.

Diameter: 100-1000 nm

30–100 nm

>1



Lawson et al. J Endocrinol 2016;228:R57-71

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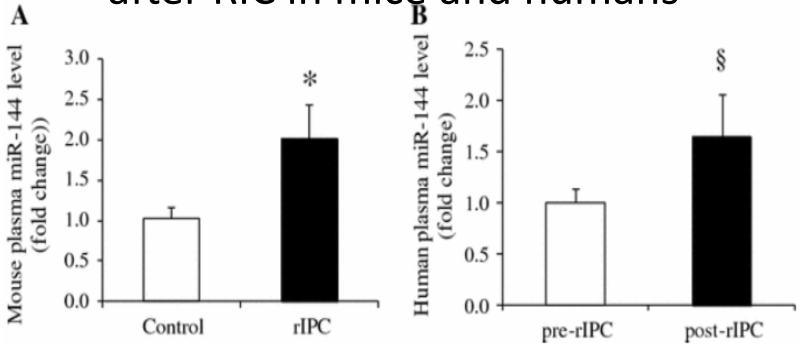
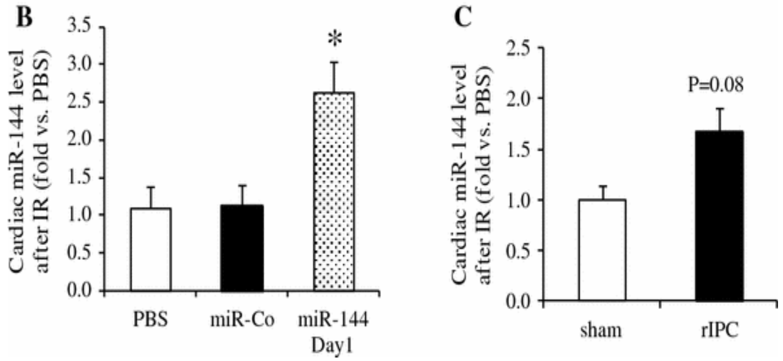
RIC, miRNA-144 and cardioprotection

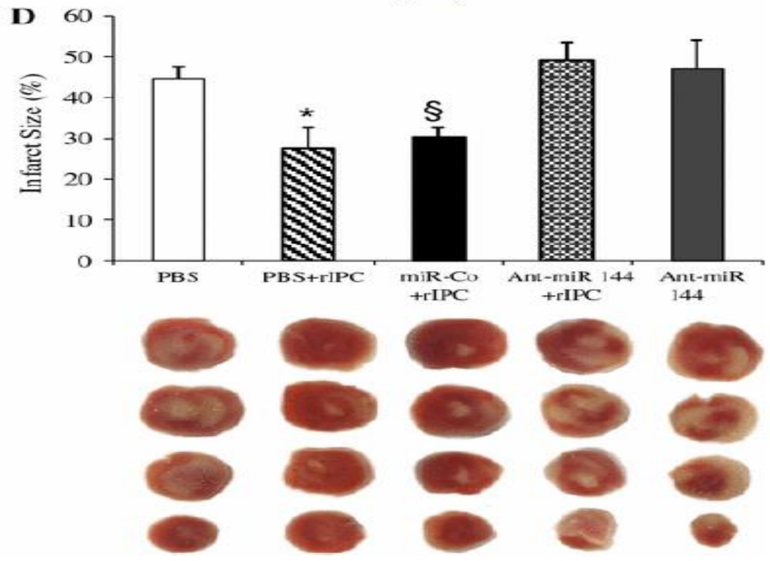
Circulating miRNA-144 increases after RIC in mice and humans



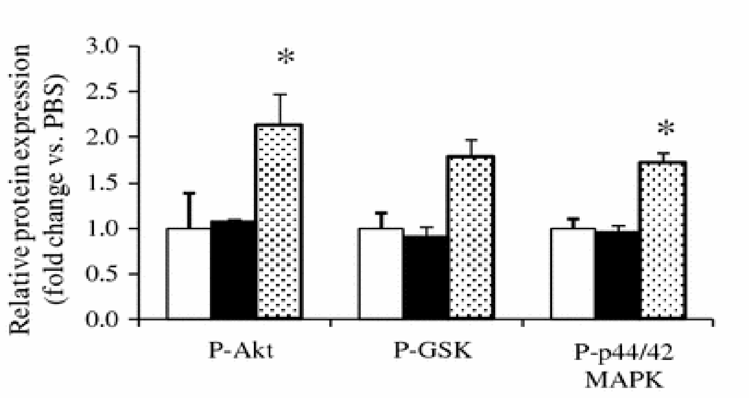
Myocardial miRNA-144 are increased after miRNA-144 adm. and RIC



Cardioprotection by RIC is abrogated by antisense miRNA-144 oligonucleotide

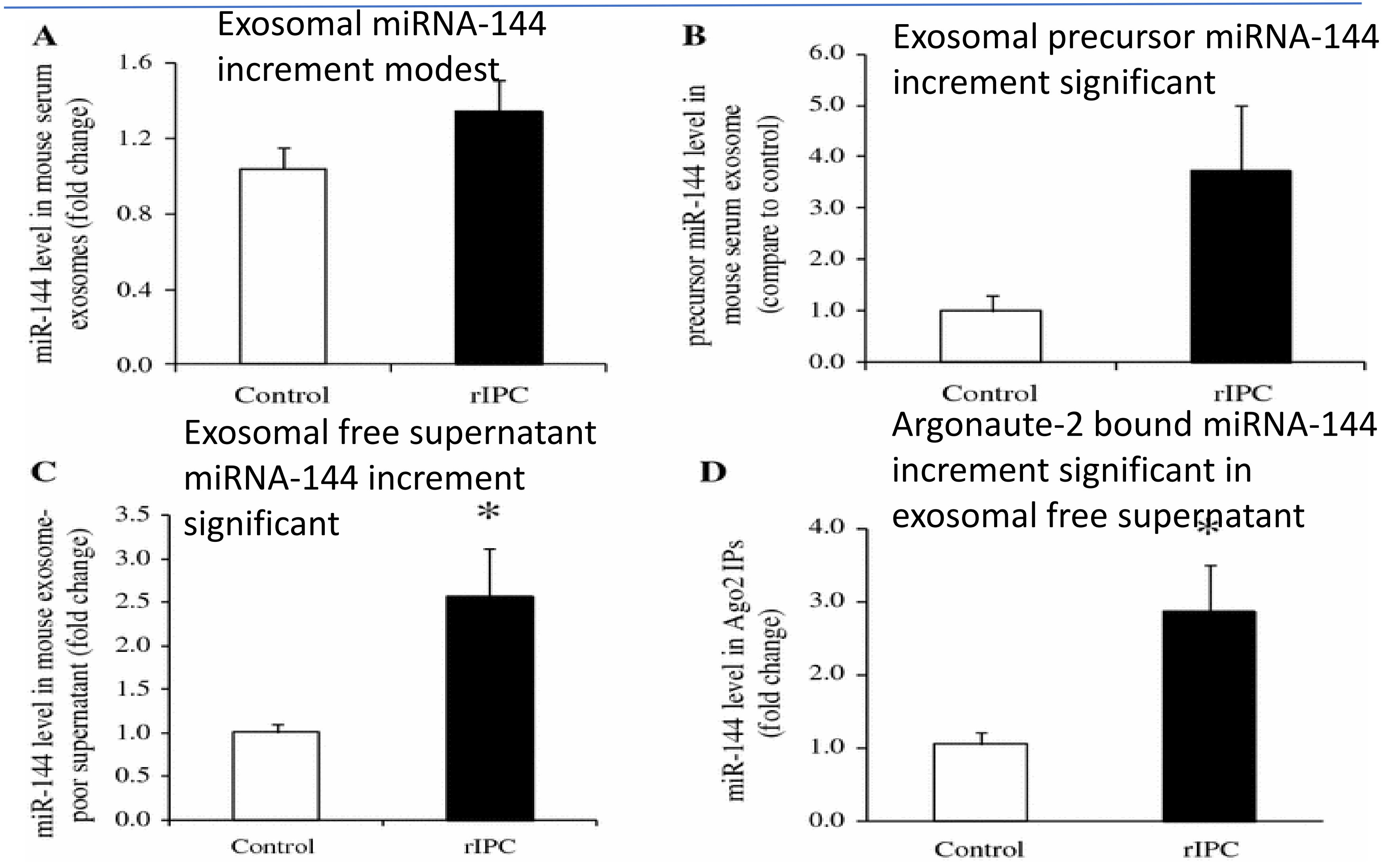


miRNA-144 upregulates cardioprotective signaling pathways



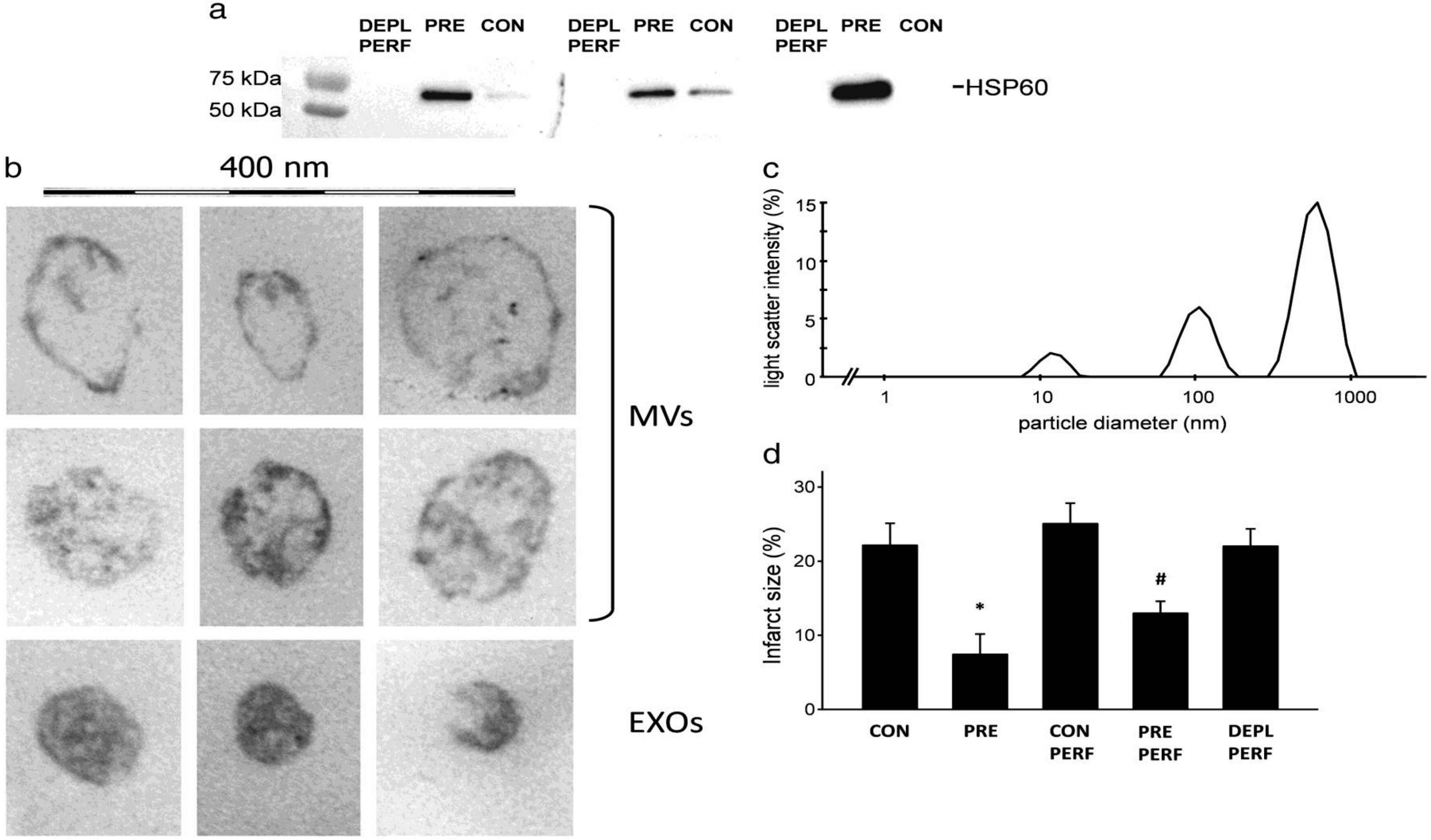
Li et al. Basic Res Cardiol 2014;109:423

miRNA-144 transport in exosomes after RIC?



Li et al. Basic Res Cardiol 2014;109:423

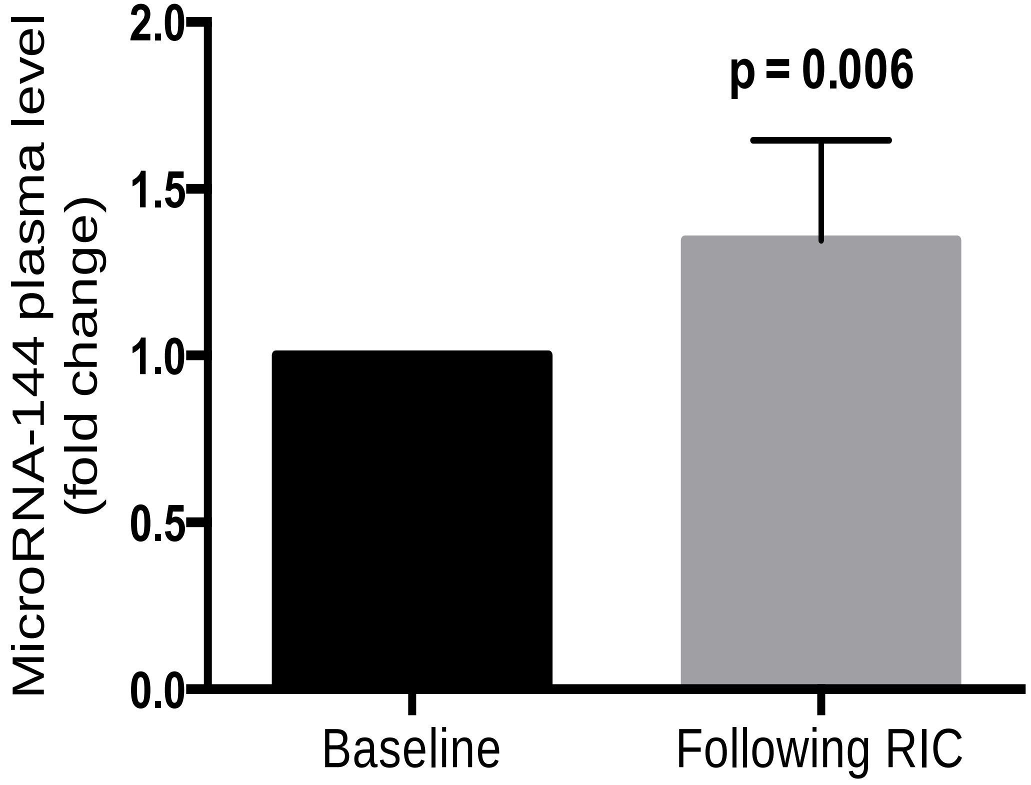
Extracellular vesicles are cardioprotective



Giricz et al. *J Mol Cell Cardiol* 2014;68:75-78

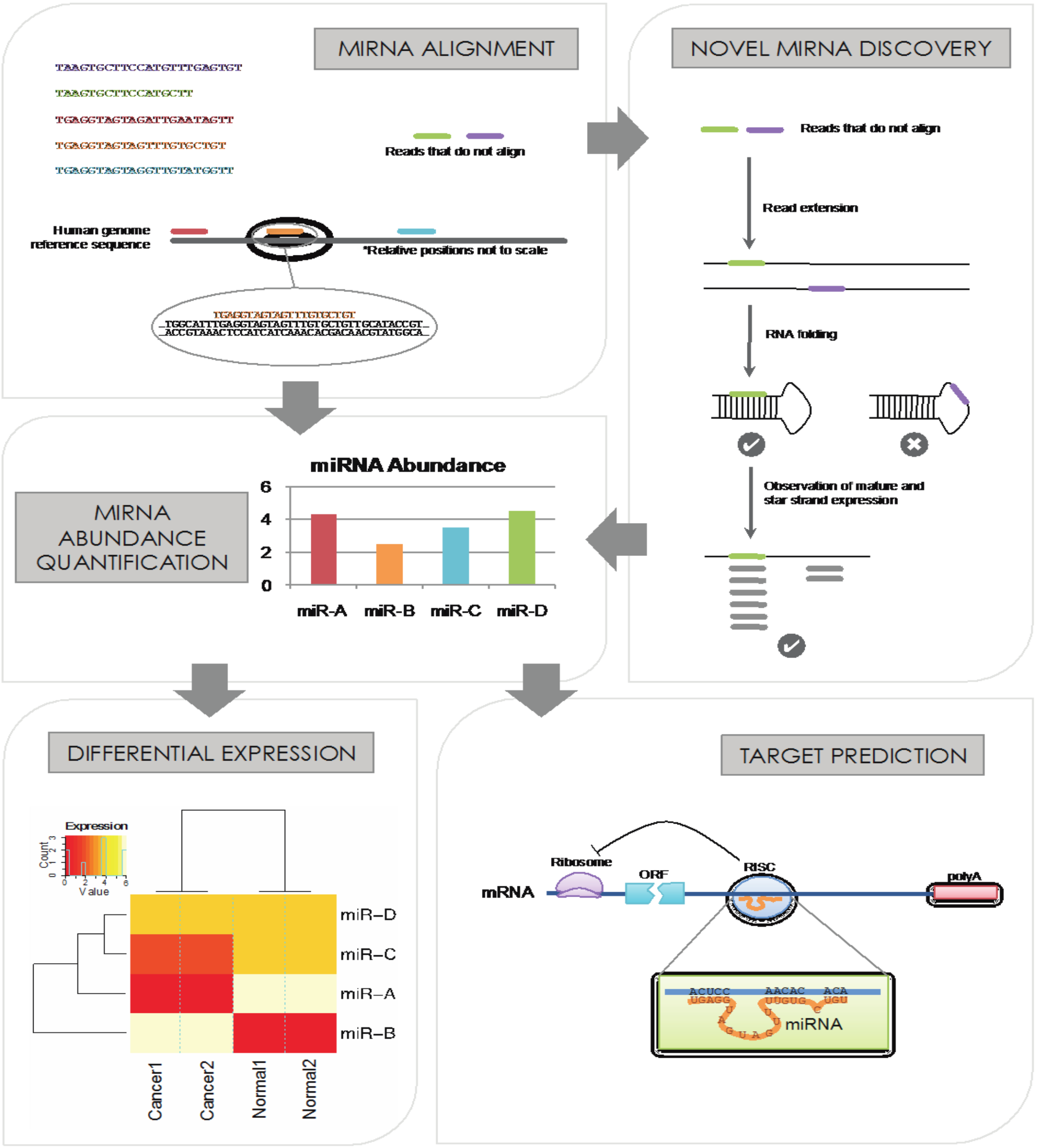
miRNA-144 after RIC in patients stable coronary artery disease

miRNA-144 increases in plasma after RIC in patients with IHD



Pryds et al. J Nucl Cardiol 2017, in press

miRNA sequencing analysis

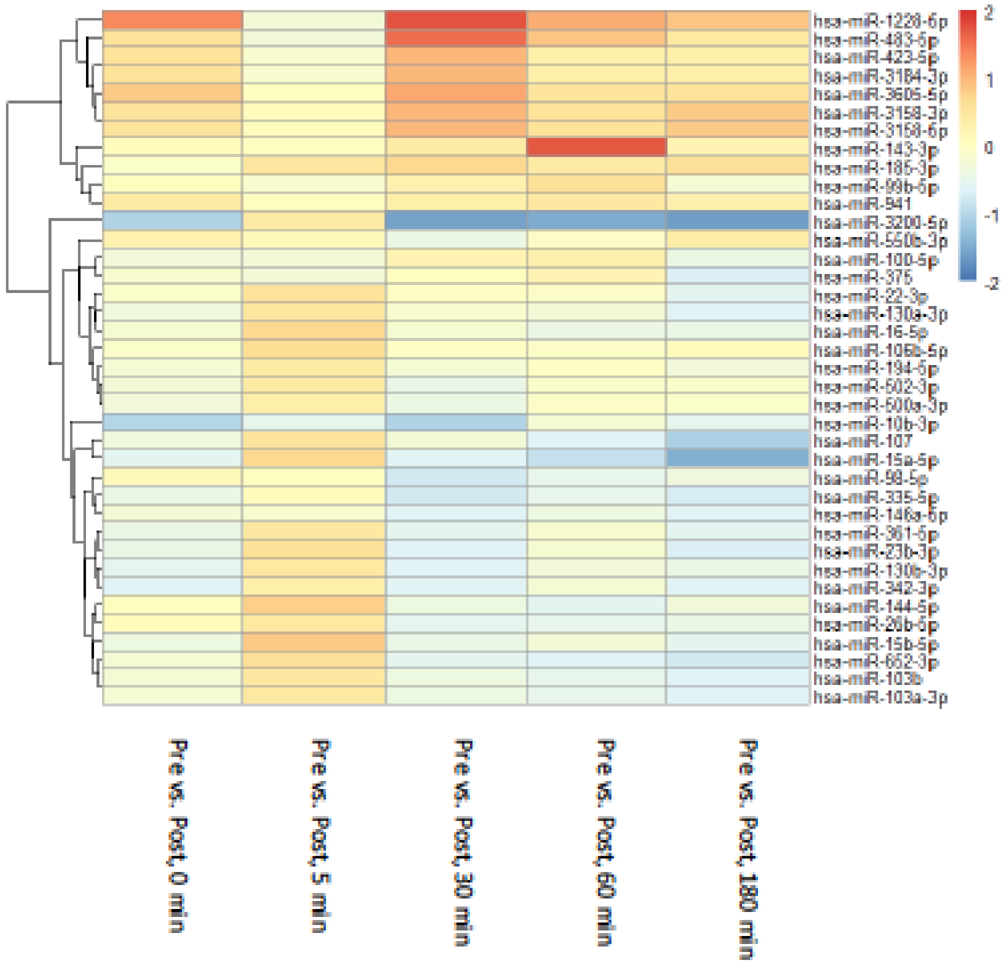


Differential expression analysis before and after RIC in healthy volunteers

Increased 30 min, post RIC

Increased 60 min, post RIC

Increased 5 min, post RIC
->is this an initial burst release of the tissue stimulated by RIC???



Just et al. 2017 In prep

DE miRNA, counts and p-values

38 DE miRNAs

	baseMean	pvalue	padj
hsa-miR-941	2182.305414	0.010282998	0.094585073
hsa-miR-423-5p	128353.2262	0.000324866	0.011571566
hsa-miR-146a-5p	45577.41529	0.01188406	0.098199861
hsa-miR-130a-3p	870.1369018	5.82E-05	0.006090425
hsa-miR-99b-5p	8206.439319	0.004206367	0.047171398
hsa-miR-23b-3p	1442.056843	0.003479627	0.040466778
hsa-miR-194-5p	11548.07017	0.011784742	0.098199861
hsa-miR-10b-3p	170.3068188	0.003399977	0.040466778
hsa-miR-26b-5p	86796.01536	0.004847531	0.050737493
hsa-miR-3184-3p	128353.2262	0.000324866	0.011571566
hsa-miR-107	8399.934335	0.000689574	0.016655869
hsa-miR-22-3p	107810.6484	0.000961823	0.020134158
hsa-miR-103b	23271.45364	0.000368521	0.011571566
hsa-miR-3605-5p	133.0942992	0.011367609	0.098199861
hsa-miR-15a-5p	3116.809603	0.001541715	0.026894357
hsa-miR-98-5p	4507.765982	0.001129746	0.022127632
hsa-miR-3200-5p	188.938684	0.001197993	0.022127632
hsa-miR-185-3p	451.4076618	0.004587007	0.049666218
hsa-miR-375	18727.50688	0.002842002	0.040466778
hsa-miR-16-5p	54221.41396	0.000242446	0.011571566
hsa-miR-130b-3p	680.7225572	0.000159799	0.011571566
hsa-miR-342-3p	1101.715332	0.008701458	0.085383056
hsa-miR-652-3p	3056.692927	0.001919366	0.030134053
hsa-miR-100-5p	19870.20135	0.002218999	0.033179315
hsa-miR-143-3p	59657.02312	0.00189316	0.030134053
hsa-miR-483-5p	541.6993444	2.04E-06	0.000641843
hsa-miR-103a-3p	23271.45364	0.000368521	0.011571566
hsa-miR-144-5p	2848.681108	0.000860251	0.019294207
hsa-miR-550b-3p	1073.589544	0.010542922	0.094585073
hsa-miR-502-3p	1656.803742	0.000321534	0.011571566
hsa-miR-15b-5p	5424.877172	0.000614626	0.016082712
hsa-miR-3158-3p	4995.640688	0.003362776	0.040466778
hsa-miR-3158-5p	4975.696087	0.003277898	0.040466778
hsa-miR-361-5p	2018.924614	1.88E-05	0.002946048
hsa-miR-106b-5p	4725.310902	0.009131329	0.086885981
hsa-miR-335-5p	895.4888086	0.003385672	0.040466778
hsa-miR-500a-3p	1372.329815	0.005452066	0.05522415
hsa-miR-1228-5p	349.0790112	0.000474787	0.013553002

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DE miRNAs: Overrepresentation analysis (pathways)

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Category	Subcategory	Enrichment	p-value	expected	observed
Pathways (miRWalk)	WP51 Regulation of Actin Cytoskeleton	over-represented	3.28599e-06	9.55689	24
Pathways (miRWalk)	hsa04666 Fc gamma R mediated phagocytosis	over-represented	3.28599e-06	7.82435	22
Pathways (miRWalk)	P00031 Inflammation mediated by chemokine and cytokine signaling pathway	over-represented	1.27585e-05	10607	24
Pathways (miRWalk)	P00034 Integrin signalling pathway	over-represented	1.27585e-05	10.5629	24
Pathways (miRWalk)	WP1984 Integrated Breast Cancer Pathway	over-represented	1.82949e-05	9.05389	22
Pathways (miRWalk)	WP474 Endochondral Ossification	over-represented	1.82949e-05	8.15968	21
Pathways (miRWalk)	hsa04140 Regulation of autophagy	over-represented	1.82949e-05	2.29142	12
Pathways (miRWalk)	hsa04810 Regulation of actin cytoskeleton	over-represented	1.82949e-05	9.9481	23
Pathways (miRWalk)	hsa04350 TGF beta signaling pathway	over-represented	1.84886e-05	9.10978	22
Pathways (miRWalk)	WP15 selenium	over-represented	1.92777e-05	6.6507	19
Pathways (miRWalk)	P00016 Cytoskeletal regulation by Rho GTPase	over-represented	2.40472e-05	7.6008	20
Pathways (miRWalk)	P00052 TGF beta signaling pathway	over-represented	2.40472e-05	8.49501	21
Pathways (miRWalk)	WP53 Id Signaling Pathway	over-represented	2.40472e-05	3.01796	13
Pathways (miRWalk)	hsa03040 Spliceosome	over-represented	2.40472e-05	8.43912	21
Pathways (miRWalk)	hsa04360 Axon guidance	over-represented	2.78283e-05	8.60679	21
Pathways (miRWalk)	P00004 Alzheimer disease presenilin pathway	over-represented	3.05277e-05	8.77445	21
Pathways (miRWalk)	P00026 Heterotrimeric G protein signaling pathway Gi alpha and Gs alpha mediated pathway	over-represented	3.05277e-05	6.31537	18
Pathways (miRWalk)	WP1601 Fluoropyrimidine Activity	over-represented	3.05277e-05	4.30339	15
Pathways (miRWalk)	hsa00590 Arachidonic acid metabolism	over-represented	3.05277e-05	3.68862	14
Pathways (miRWalk)	hsa04142 Lysosome	over-represented	3.05277e-05	6.25948	18
Pathways (miRWalk)	P00054 Toll receptor signaling pathway	over-represented	3.18963e-05	5.64471	17
Pathways (miRWalk)	P00012 Cadherin signaling pathway	over-represented	4.80607e-05	7.32136	19
Pathways (miRWalk)	hsa04062 Chemokine signaling pathway	over-represented	4.96089e-05	10004	22
Pathways (miRWalk)	hsa04930 Type II diabetes mellitus	over-represented	5.10942e-05	5.86826	17
Pathways (miRWalk)	hsa05211 Renal cell carcinoma	over-represented	5.10942e-05	10.0699	22
Pathways (miRWalk)	WP2018 RANKL RANK Signaling Pathway	over-represented	5.29453e-05	7.43313	19
Pathways (miRWalk)	WP231 TNF alpha Signaling Pathway	over-represented	5.61776e-05	8.32735	20
Pathways (miRWalk)	hsa04144 Endocytosis	over-represented	5.61776e-05	11.1776	23
Pathways (miRWalk)	P00035 Interferon gamma signaling pathway	over-represented	5.69967e-05	4.02395	14
Pathways (miRWalk)	WP2035 FSH signaling pathway	over-represented	5.69967e-05	5.30938	16
Pathways (miRWalk)	WP314 FAS pathway and Stress induction of HSP regulation	over-represented	5.69967e-05	6.76248	18
Pathways (miRWalk)	WP75 Toll Like Receptor signaling	over-represented	5.69967e-05	7.54491	19
Pathways (miRWalk)	WP176 Folate Metabolism	over-represented	6.72926e-05	6.09182	17
Pathways (miRWalk)	hsa04662 B cell receptor signaling pathway	over-represented	8.00719e-05	6.93014	18
Pathways (miRWalk)	WP366 TGF beta Signaling Pathway1	over-represented	8.40146e-05	11513	23
Pathways (miRWalk)	hsa05016 Huntingtons disease	over-represented	0.000108637	9.66866	21
Pathways (miRWalk)	WP138 Androgen receptor signaling pathway	over-represented	0.000125379	12.9102	24
Pathways (miRWalk)	WP384 Apoptosis Modulation by HSP70	over-represented	0.000125379	2.62675	11
Pathways (miRWalk)	WP560 TGF beta Signaling Pathway2	over-represented	0.000125379	7.99202	19
Pathways (miRWalk)	hsa00380 Tryptophan metabolism	over-represented	0.000147262	2.68263	11
Pathways (miRWalk)	hsa05110 Vibrio cholerae infection	over-represented	0.000147262	5.75649	16
Pathways (miRWalk)	hsa00531 Glycosaminoglycan degradation	over-represented	0.000154391	1.34132	8
Pathways (miRWalk)	P00049 Parkinson disease	over-represented	0.000157764	8.15968	19

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DE miRNAs: Overrepresentation analysis (target genes)

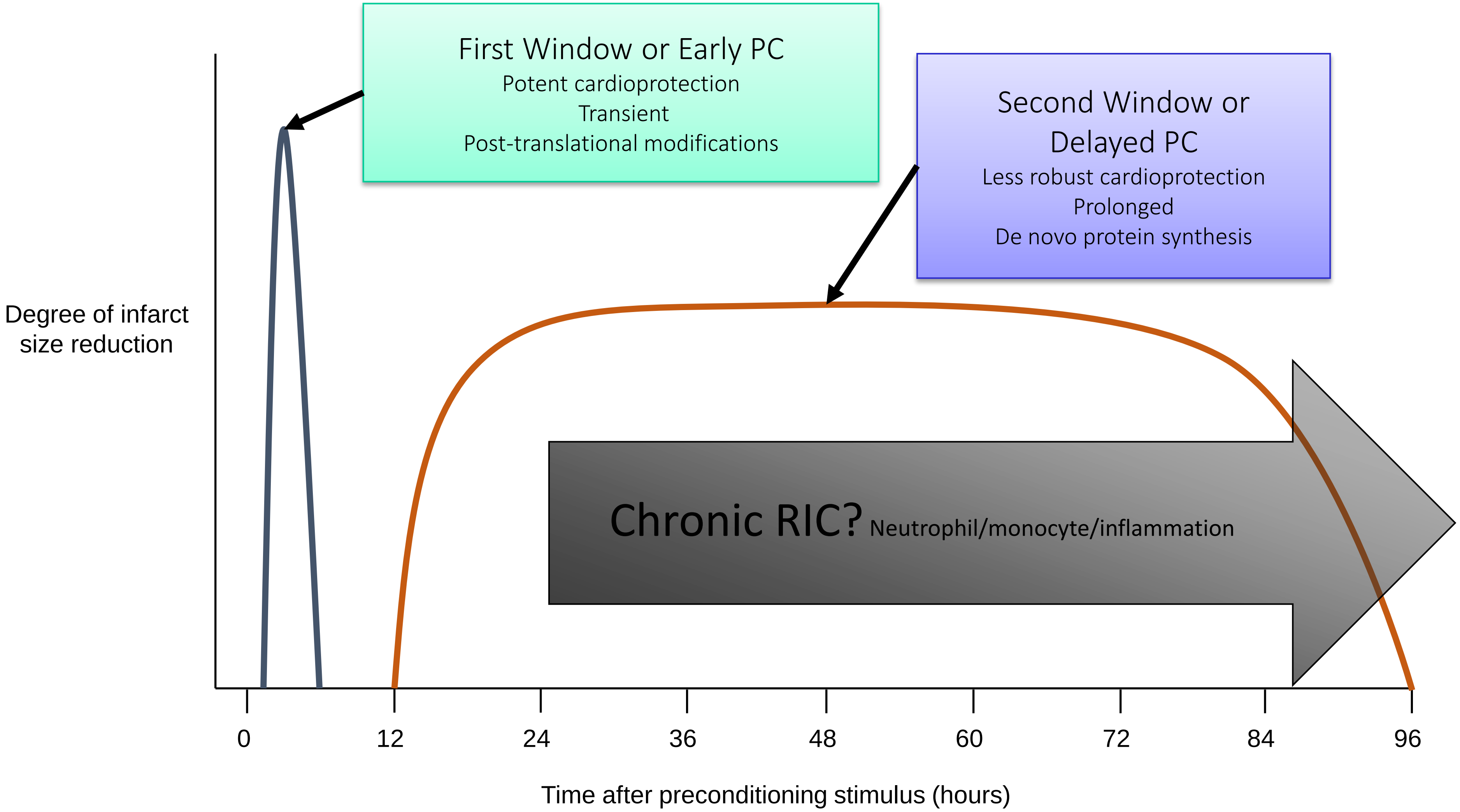
P-value

	Category	Subcategory		Enrichment	p-value	expected	observed	miRNAs/precursors
1	Target genes (miRTarbase)	PDK4		over-represented	0.00894596	0.208633	4	hsa-miR-26b-5p; hsa-miR-16-5p; hsa-miR-103a-3p; hsa-miR-335-5p
2	Target genes (miRTarbase)	SMAD7		over-represented	0.00894596	0.573741	6	hsa-miR-26b-5p; hsa-miR-98-5p; hsa-miR-16-5p; hsa-miR-100-5p; hsa-miR-103a-3p; hsa-miR-15b-5p
3	Target genes (miRTarbase)	TNFSF9		over-represented	0.00894596	0.208633	4	hsa-miR-26b-5p; hsa-miR-98-5p; hsa-miR-16-5p; hsa-miR-335-5p
4	Target genes (miRTarbase)	CDK17		over-represented	0.0129327	0.260791	4	hsa-miR-98-5p; hsa-miR-16-5p; hsa-miR-103a-3p; hsa-miR-335-5p
5	Target genes (miRTarbase)	GNS		over-represented	0.0129327	0.260791	4	hsa-miR-23b-3p; hsa-miR-107; hsa-miR-103a-3p; hsa-miR-335-5p
6	Target genes (miRTarbase)	HSPA1A		over-represented	0.0129327	0.260791	4	hsa-miR-146a-5p; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-335-5p
7	Target genes (miRTarbase)	PLSCR4		over-represented	0.0129327	0.260791	4	hsa-miR-16-5p; hsa-miR-103a-3p; hsa-miR-15b-5p; hsa-miR-335-5p
8	Target genes (miRTarbase)	RAD51C		over-represented	0.0129327	0.260791	4	hsa-miR-26b-5p; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-100-5p
9	Target genes (miRTarbase)	SMOC2		over-represented	0.0129327	0.260791	4	hsa-miR-26b-5p; hsa-miR-16-5p;

Number of time observed

	Category	Subcategory		Enrichment	p-value	expected	observed	miRNAs/precursors
1	Target genes (miRTarbase)	EEF1A1		over-represented	0.0395211	2.19065	7	hsa-miR-23b-3p; hsa-miR-26b-5p; hsa-miR-16-5p; hsa-miR-652-3p; hsa-miR-100-5p; hsa-miR-15b-5p; hsa-miR-106b-5p
2	Target genes (miRTarbase)	VEGFA		over-represented	0.0364171	2.13849	7	hsa-miR-107; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-15b-5p; hsa-miR-361-5p; hsa-miR-106b-5p; hsa-miR-335-5p
3	Target genes (miRTarbase)	ACTG1		over-represented	0.0298026	1.46043	6	hsa-miR-423-5p; hsa-miR-99b-5p; hsa-miR-16-5p; hsa-miR-342-3p; hsa-miR-652-3p; hsa-miR-361-5p
4	Target genes (miRTarbase)	CCND2		over-represented	0.0298026	1.2518	6	hsa-miR-423-5p; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-342-3p; hsa-miR-106b-5p; hsa-miR-335-5p
5	Target genes (miRTarbase)	CCNE1		over-represented	0.0158562	0.886691	6	hsa-miR-26b-5p; hsa-miR-107; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-103a-3p; hsa-miR-15b-5p
6	Target genes (miRTarbase)	DICER1		over-represented	0.0293702	1.14748	6	hsa-miR-130a-3p; hsa-miR-107; hsa-miR-98-5p; hsa-miR-16-5p; hsa-miR-130b-3p; hsa-miR-103a-3p
7	Target genes	PLAG1		over-represented	0.0158562	0.886691	6	hsa-miR-26b-5p;

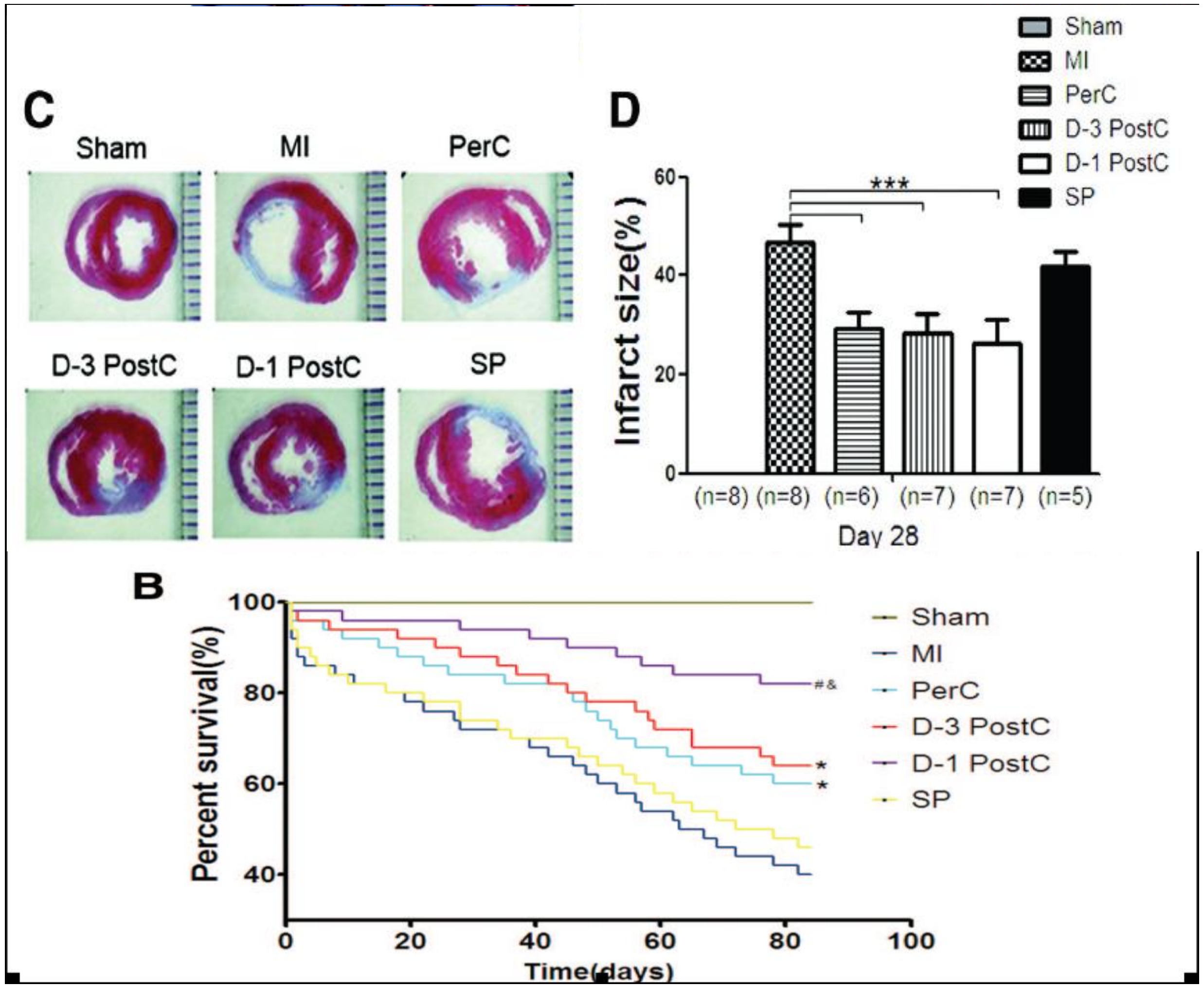
Phases of Protection: Beyond IR Protection?



Adapted from Hausenloy et al. Preconditioning the myocardium: from cellular physiology to clinical cardiology. Physiol. Rev. 2003

Effect of extended period of conditioning

Repeated rIPostC improves survival in a rat model of myocardial infarction despite absence of further reduction of infarct size compared to rIPerC alone



Wei et al. *Circ Res.* 2011;108:1220-5.

Conclusion

- RIC and strenuous physical exercise induce cardioprotection (partially) mediated through blood borne factors
- RIC may improve aerobic physical performance
- RIC does not improve muscle strength
- miRNA is a likely involved in the pathway
- Is low intensity physical exercise cardioprotective?