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

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Concept of remote preconditioning

Intraorgan remote

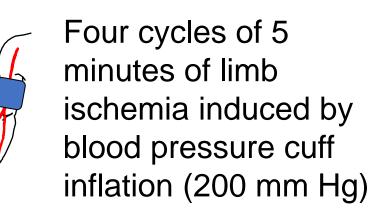


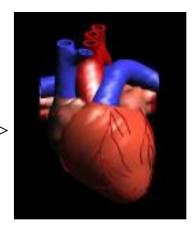
Occlusion of CX Infarct size



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

Interorgan remote

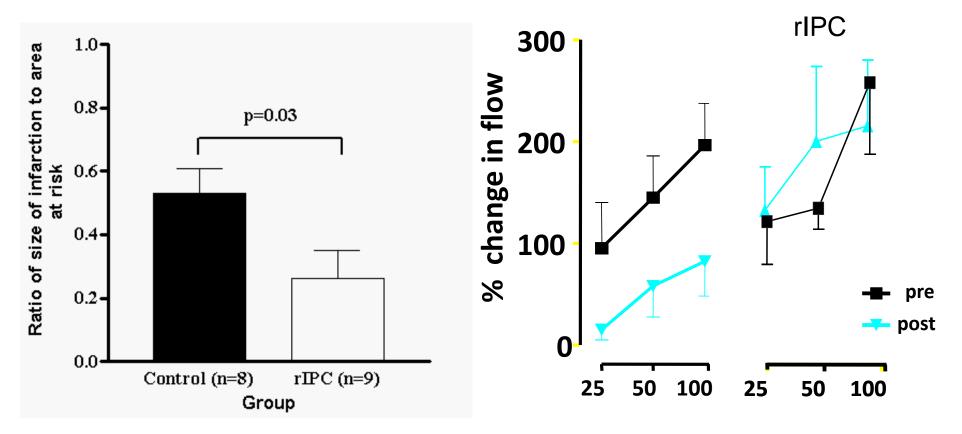




Birnbaum Y et al. *Circulation* 1997;96:1641-6 Kharbanda R et al. *Circulation* 2002;106:2881-3

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

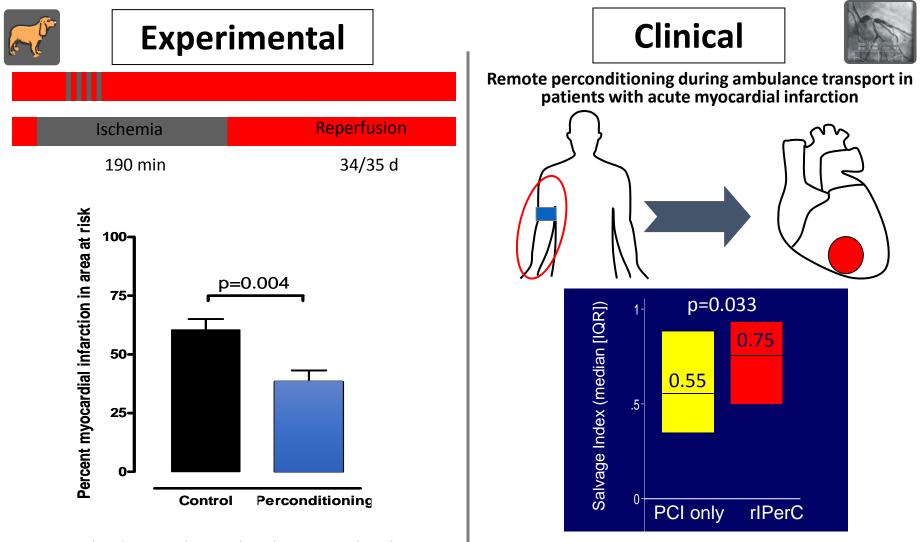
- Coming from IPC
- The concept
- Mimicking claudication?
- The warm-up phenomenon

| 5 min. |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Inflation | Deflation | Inflation | Deflation | Inflation | Deflation | Inflation |



Inflates to 200 mm Hg

Remote conditioning



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

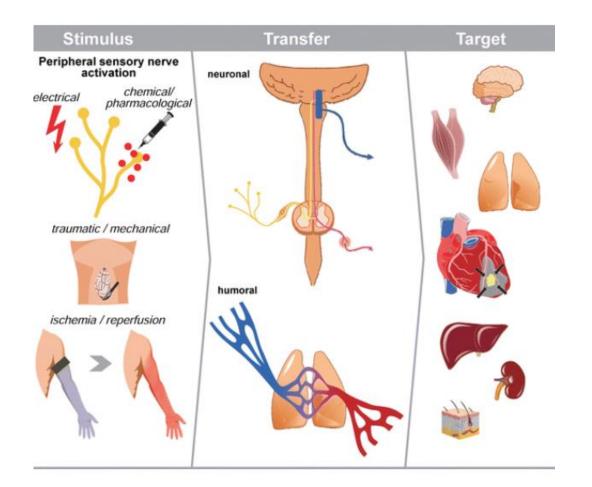
Efficacy of RIC in humans

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

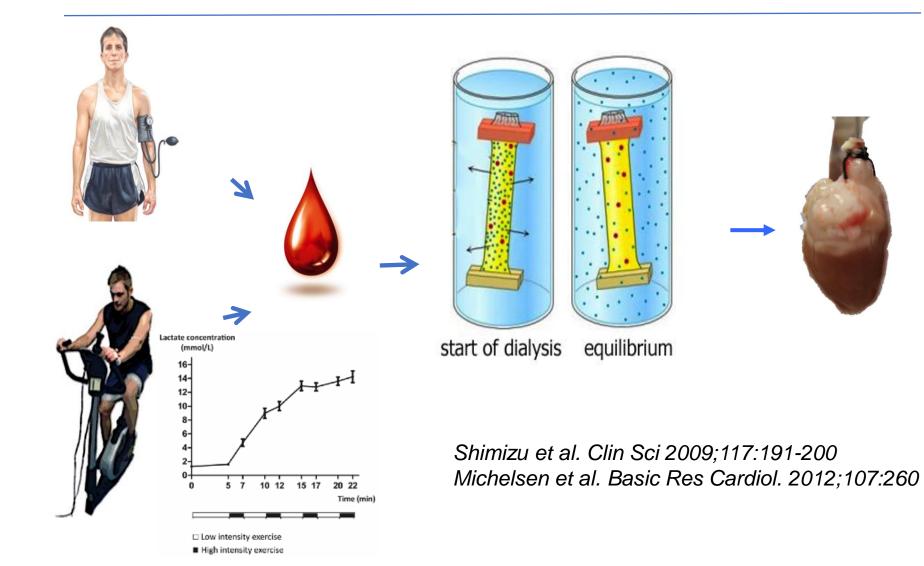
Schmidt, Rasmussen, Bøtker. J Cardiovasc Pharmacol Ther 2017, 22:302-309

How does RIC work?

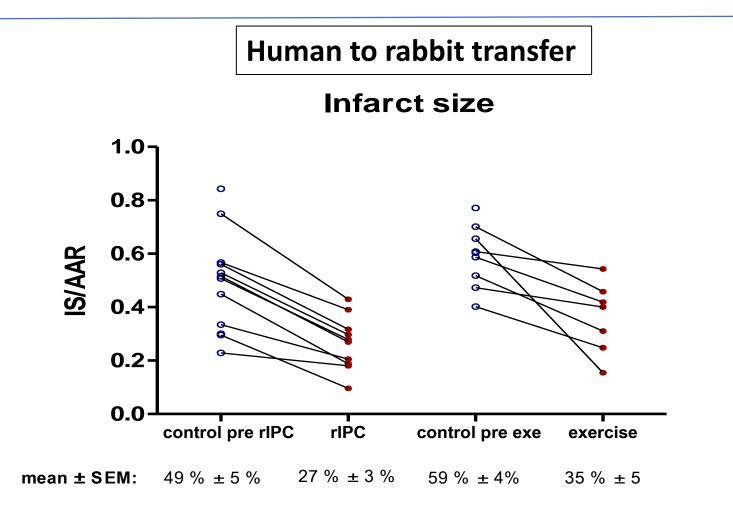
- Multiple triggers
- Parallel pathways
- Dynamic course of protection
- Systemic effects
- Trigger, mediator, effector Too simplified?



Dialysate as a bioassay for RIC: Human to rabbit transfer

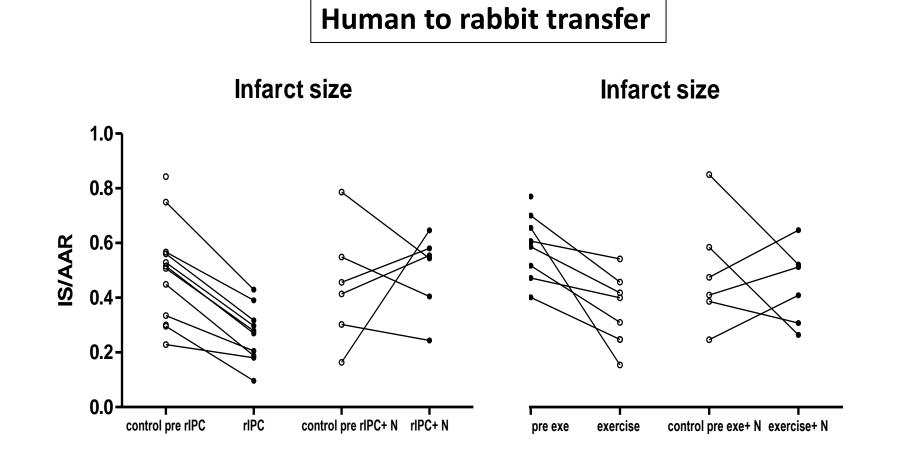


Cardioprotection with RIC and exercise



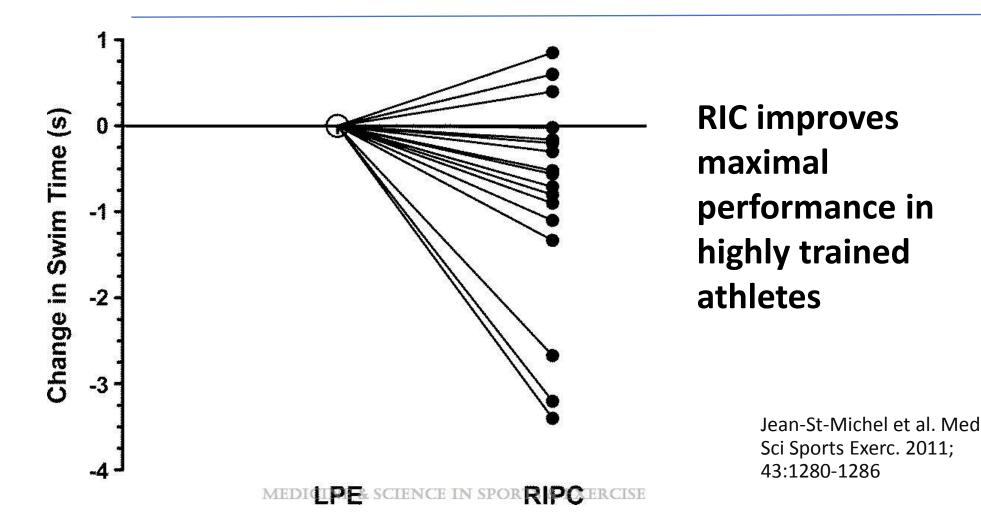
Michelsen et al. Basic Res Cardiol. 2012;107:260

AARHUS UNIVERSITY Mediating substance: endogenous opioids?



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

Can biological performance and resilience be enhanced or extended?



Effect of RIC on aerobic/anaerobic performance

Sports Setting	Design	Algorithm	Outcomes						
Aerobic: Elite swimmers, 100 m freestyle (1)	40 athletes, crossover design	4 x 5/5 mins	RIPC improves swim performance by 0.6 seconds per 100 metres swim distance						
Level of improvement app	roximately equal to	18 months of training	-						
Aerobic: Cycling (2)	15 athletes, crossover design	3 x 5/5 mins	RIC improves cycling performance. Oxygen consumption increases 3%, power output increased 1.6%.						
Oxygen consumption impr	ovement comparab	le to ~1 month of altit	ude training.						
Aerobic: Running, regular (non- elite) exercisers (3)	13 volunteers cross-over trial	3 x 5/5 mins	30 second reduction in 5K time in regular, non-elite, exercisers						
Aerobic/Submaximal performance: Cycling (4)	12 athletes cross-over trial	3 x 5/5 mins	RIC did not improve submaximal performance						
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.									

Anaerobic: Land-based sprinting/ Team sport athletes (5)	25 athletes cross-over trial	3 x 5/5 mins	No significant effects of the preconditioning treatment were observed on sprint speed (P < .05) at any of the split timings.
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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.

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

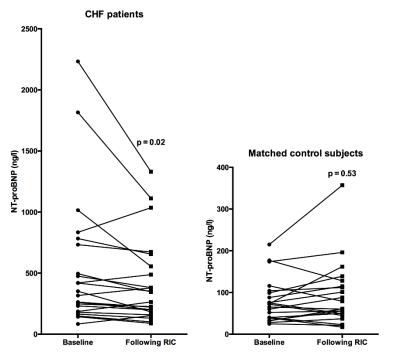
	BASELINE	Follow-up	CI	P-value
Patients with CIHF	DAJELINE			
Peak cardiopulmonary exercise capacity:				
- Workload (W/kg)	1.6 ± 0.31	1.6 ± 0.33	-0.02 to 0.08	p=0.26
- Oxygen uptake (ml/kg/min)	19.9	20.1		p=0.59
Leg Extensor Power Rig (W/kg)	2.3 ± 0.8	2.5 ± 0.8	0.02 to 0.21	p=0.02
Control subjects				
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

AARHUS UNIVERSITY NTPro-BNP and subgroup



	Baseline	Follow-up	CI	p-value
Patients with CHF ar	nd NT-proBN	IP > 350 ng/l (n=11)	
_VEF (%)	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 AutoRICTM (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).

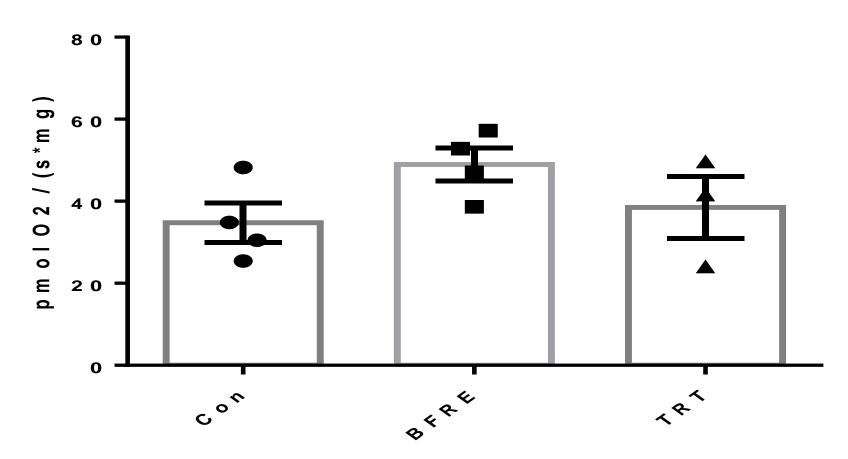


Traditional Resistance Exercise (TRT) – included to allow BFRE versus TRT comparison: Conventional moderate to heavy intensive resistance exercise (i.e., 3-4 sets of 10-15 repetitions in a isolated knee extensor apparatus, with a load equalling 15RM and inter-set recovery of 3 minutes).



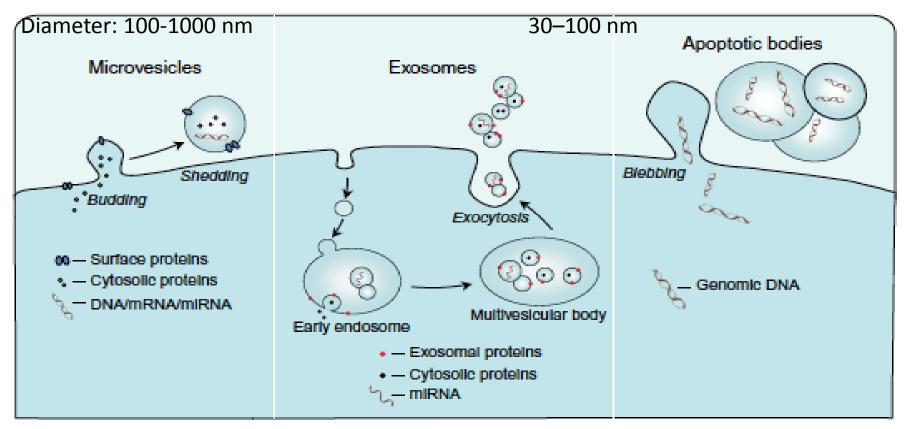
Influence of training and BFRE on mitochondrial respiration





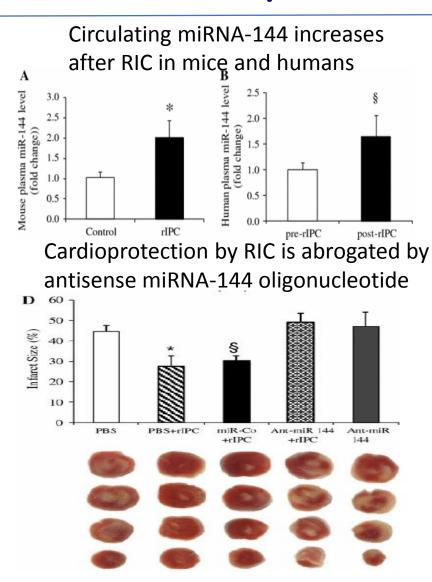
AARHUS UNIVERSITY Interorgan communication and transfer

- 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.

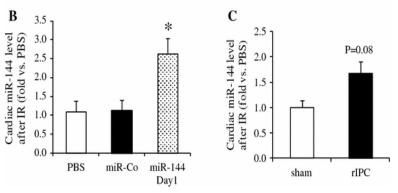


Lawson et al. J Endocrinol 2016;228:R57-71

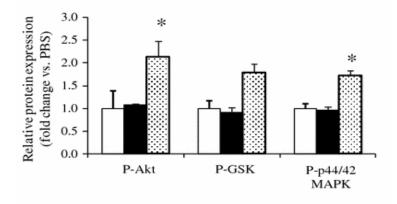
AARHUS UNIVERSITY RIC, miRNA-144 and cardioprotection



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

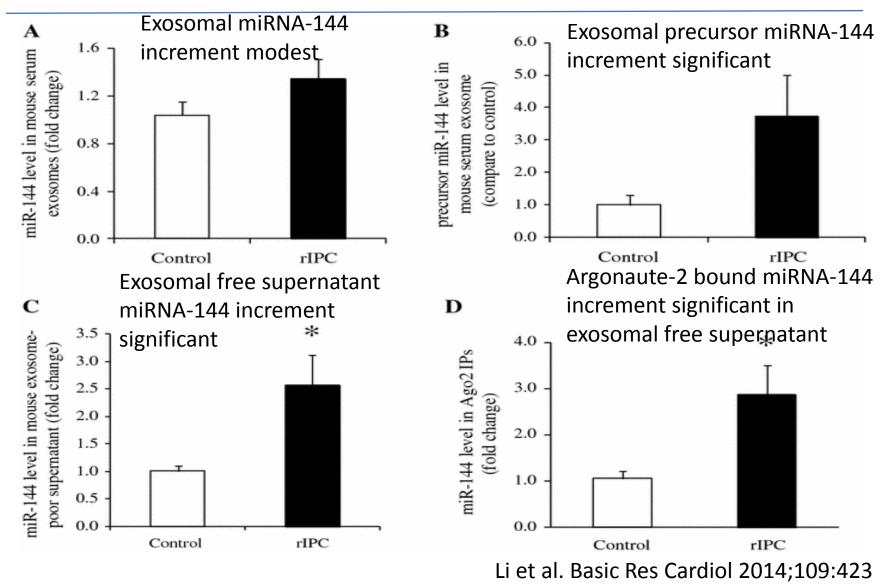


miRNA-144 upregulates cardioprotective signaling pathways

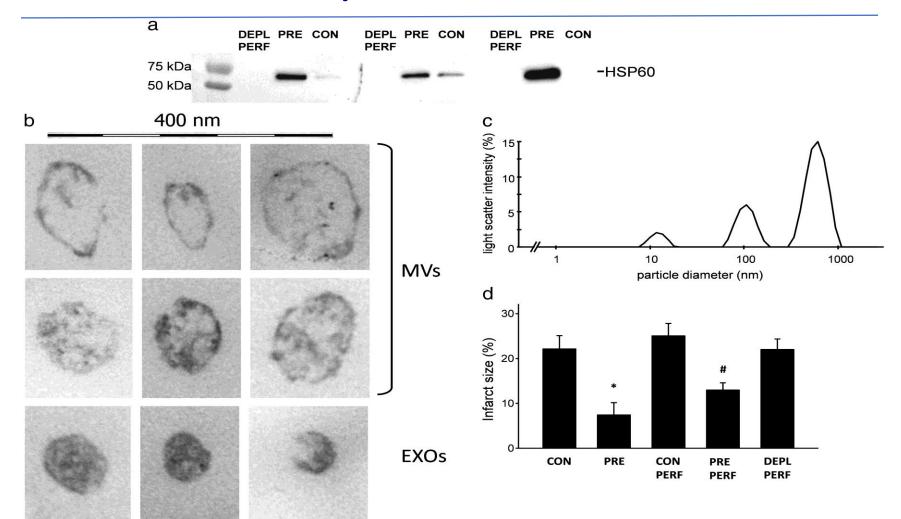


Li et al. Basic Res Cardiol 2014;109:423

miRNA-144 transport in exosomes after RIC?



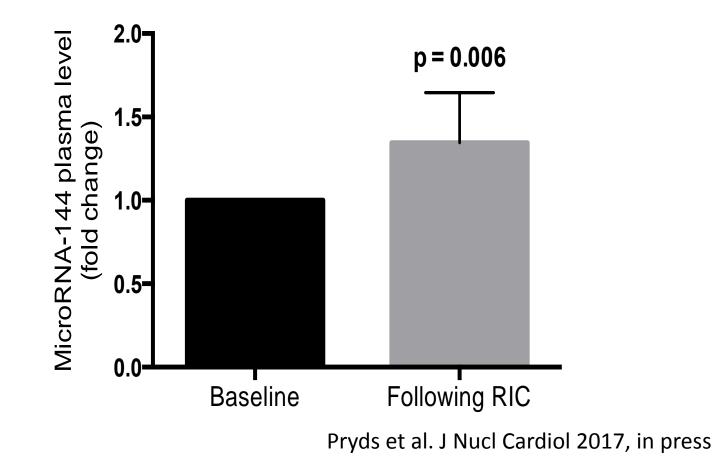
Extracellular vesicles are cardioprotective



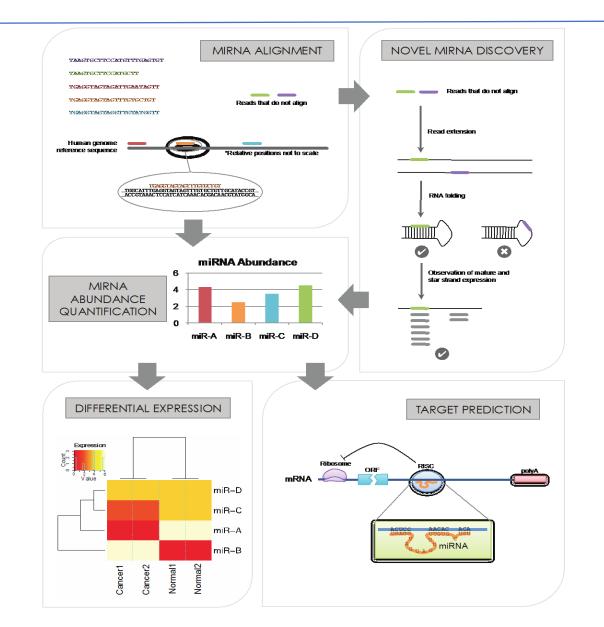
Giricz et al. J Mol Cell Cardiol 2014;68:75-78

miRNA-144 after RIC in patients stable coronary artery disease

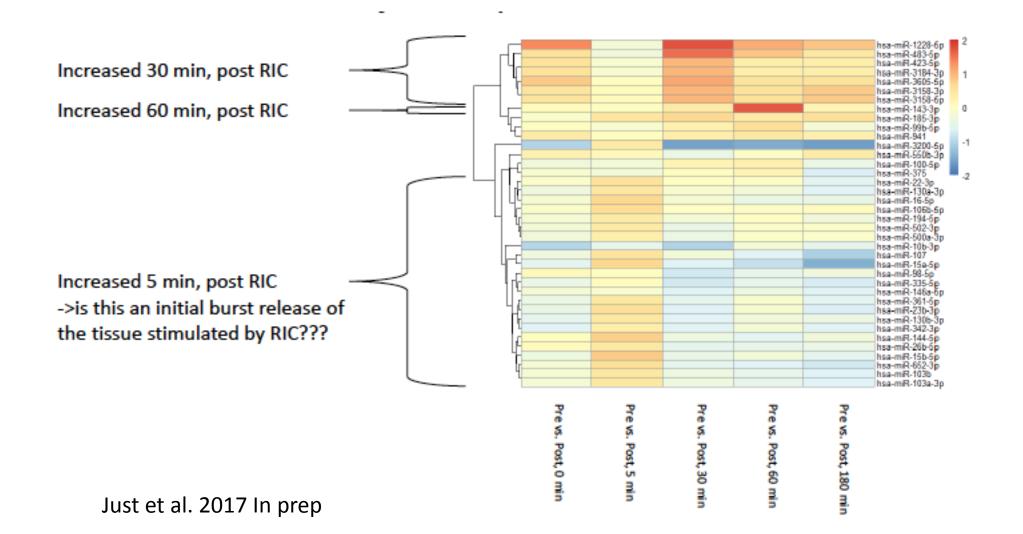
miRNA-144 increases in plasma after RIC in patients with IHD



miRNA sequencing analysis



Differential expression analysis before and after RIC in healthy volunteers



DE miRNA, counts and p-values

38 DE miRNAs

has-miR-941 2182.305.414 0.01028298 0.094585073 has-miR-1423-5p 128353.2262 0.000324866 0.011571566 has-miR-146a-5p 45577.41529 0.01184406 0.086199661 has-miR-199b-5p 8206.439319 0.004206367 0.004708627 has-miR-199b-5p 8206.439319 0.004206367 0.004046778 has-miR-194-5p 11548.07017 0.011784722 0.098199861 has-miR-10b-3p 170.3066188 0.003399977 0.040466778 has-miR-10b-3p 170.3066188 0.003399977 0.040466778 has-miR-10b-3p 128353.2262 0.000524866 0.011571566 has-miR-107 8399.934335 0.00068574 0.01665589 has-miR-108 23271.45364 0.00068521 0.011317156 has-miR-103b 23271.45364 0.00058521 0.011317156 has-miR-103b 23271.45364 0.00058521 0.0112171366 has-miR-103b 23271.45364 0.000129746 0.02127632 has-miR-105-5p 3116.09603 0.0011541715 0.02684357 has-miR-105-5p 182.07.755982 0.001129746 0.02127632 has-miR-105-5p 145.076618 0.00242402 0.40466778 has-miR-105-5p 145.076568277<			baseMean		pvalue	padj
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hsa-miR-3184-3p 128353.2262 0.000324866 0.011571566 hsa-miR-107 8399.934335 0.00069574 0.01655869 hsa-miR-103b 028271.45364 0.000951823 0.020134158 hsa-miR-103b 023271.45364 0.000368521 0.011571566 hsa-miR-103b 023271.45364 0.000368521 0.011571566 hsa-miR-103b 0.001587609 0.098199861 hsa-miR-105-5p 133.0942992 0.01129746 0.022127632 hsa-miR-155-5p 4507.765982 0.001129746 0.022127632 hsa-miR-155-3p 451.407.6618 0.004587007 0.049666218 hsa-miR-165p 54221.41396 0.000242446 0.011571566 hsa-miR-130b-3p 680.7225572 0.0001919999 0.011571566 hsa-miR-142-3p 1101.715322 0.002218999 0.03314053 hsa-miR-100-5p 19870.20135 0.002218999 0.03134053 hsa-miR-143-3p 59657.02312 0.001936521 0.011571566 hsa-miR-144-5p 2848.681108 0.000368521 0.011571566 hsa-miR-150-5p 1073.598544 0.000368521 0.011571566		hsa-miR-10b-3p		170.3068188	0.00339997	7 0.040466778
hsa-miR-107 8399.934335 0.000689574 0.016655869 hsa-miR-22-3p 107810.6484 0.000961823 0.021134158 hsa-miR-103b 23271.45364 0.000368521 0.011571566 hsa-miR-3605-5p 133.0942992 0.011367609 0.098199861 hsa-miR-3605-5p 1316.809603 0.001541715 0.026894357 hsa-miR-15a-5p 4507.765982 0.001197993 0.022127632 hsa-miR-3200-5p 188.938684 0.001197993 0.022127632 hsa-miR-15a-5p 4507.765982 0.001197993 0.022127632 hsa-miR-15a-5p 18727.50688 0.002842002 0.040466778 hsa-miR-165p 54221.41396 0.000159799 0.011571566 hsa-miR-130b-3p 660.0725572 0.000159799 0.011571566 hsa-miR-143-5p 19870.20135 0.002218999 0.03134053 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-144-5p 2484.681108 0.000368521 0.011571566 hsa-miR-103a-3p 123271.45364 0.000368521		hsa-miR-26b-5p		86796.01536	0.00484753	1 0.050737493
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 0.02684357 hsa-miR-15a-5p 4507.765982 0.001129746 0.022127632 hsa-miR-3200-5p 188.938644 0.001587007 0.049666218 hsa-miR-165.5p 451.4076618 0.00242446 0.011571566 hsa-miR-135 18727.50688 0.00242446 0.011571566 hsa-miR-130b-3p 6680.722572 0.0001458 0.063313056 hsa-miR-143-3p 101.715332 0.0001458 0.03313051 hsa-miR-165.2p 19870.20135 0.00218999 0.03314053 hsa-miR-433.5p 591657.02312 0.00189316 0.030134053 hsa-miR-143.3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-165.2p 1073.589544 0.000368521 0.011571566 <td></td> <td>hsa-miR-3184-3p</td> <td></td> <td>128353.2262</td> <td>0.00032486</td> <td>6 0.011571566</td>		hsa-miR-3184-3p		128353.2262	0.00032486	6 0.011571566
hsa-miR-103b 23271.45364 0.000368521 0.011571566 hsa-miR-15a-5p 133.0942992 0.011367609 0.088198861 hsa-miR-15a-5p 3116.809603 0.001541715 0.026894357 hsa-miR-3200-5p 4507.765592 0.001129746 0.022127632 hsa-miR-185-3p 451.4076618 0.004567007 0.049666218 hsa-miR-185-3p 18727.50688 0.0002842002 0.040466778 hsa-miR-165p 54221.41396 0.002242464 0.011571566 hsa-miR-100-3p 680.7225572 0.000197999 0.011571566 hsa-miR-100-3p 680.7225572 0.000197999 0.011571566 hsa-miR-100-3p 1010.715332 0.006701458 0.063383056 hsa-miR-100-5p 19870.20135 0.00212999 0.03134053 hsa-miR-103a-3p 59657.02312 0.00189316 0.030134053 hsa-miR-505-3p 1073.589544 0.000368521 0.011571566 hsa-miR-505-3p 1656.803742 0.000368521 0.011571566 hsa-miR-505-3p 1656.803742 0.000368521 0.011571566 hsa-miR-505-3p 1656.803742 0.000321534		hsa-miR-107		8399.934335	0.00068957	4 0.016655869
hsa-miR-3605-5p 133.0942992 0.011367609 0.098199861 hsa-miR-15a-5p 3116.809603 0.001541715 0.026894357 hsa-miR-305-5p 4507.765982 0.001129746 0.022127632 hsa-miR-3200-5p 18898684 0.001197993 0.022127632 hsa-miR-355 18727.50688 0.002842002 0.040466778 hsa-miR-16-5p 54221.41396 0.002242466 0.011571566 hsa-miR-375 18727.50688 0.002842002 0.040466778 hsa-miR-16-5p 54221.41396 0.0005701458 0.085383056 hsa-miR-32-3p 10056.692927 0.001919366 0.030134053 hsa-miR-100-5p 19870.20135 0.002218999 0.03179315 hsa-miR-103-3p 5416.693444 2.04E-06 0.00641843 hsa-miR-103-3p 23271.45364 0.000360521 0.0119214207 hsa-miR-103-3p 1073.589544 0.000360521 0.011571566 hsa-miR-103-3p 1073.589544 0.000360521 0.0119214207 hsa-miR-103-3p 1073.589544 0.000360521 0.011571566 hsa-miR-1550b-3p 1073.589544 0.000321534		hsa-miR-22-3p		107810.6484	0.00096182	3 0.020134158
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 0.004867007 0.049666218 hsa-miR-185-75 18727.50688 0.002842002 0.040466778 hsa-miR-16-5p 54221.41396 0.000242446 0.011571566 hsa-miR-342-3p 1101.715332 0.000159799 0.011571566 hsa-miR-652-3p 3056.692927 0.001919366 0.030134053 hsa-miR-100-5p 19870.20135 0.002218999 0.033179315 hsa-miR-103a-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-103a-3p 1073.589544 0.000368521 0.011571566 hsa-miR-550b-3p 1073.589544 0.000361222 0.094585073 hsa-miR-155-5p 5424.877172 0.000614226 0.01068271 hsa-miR-3158-3p 4995.640688 0.003362776 0.0040466778 hsa-miR-3158-5p 4995.640688 0.00		hsa-miR-103b		23271.45364	0.00036852	1 0.011571566
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-185-5p 18727.50688 0.002842002 0.040466778 hsa-miR-130b-3p 680.7225572 0.000159799 0.011571566 hsa-miR-342-3p 1101.715332 0.00271458 0.085383056 hsa-miR-4652-3p 3056.692927 0.001919366 0.030134053 hsa-miR-130-5p 19870.20135 0.002212999 0.03179315 hsa-miR-143-3p 59657.02312 0.00189316 0.000641843 hsa-miR-143-3p 59657.02312 0.00189316 0.000641843 hsa-miR-143-3p 23271.45364 0.000368521 0.011571566 hsa-miR-163a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-50b-3p 1073.589544 0.000321534 0.011571566 hsa-miR-550-3p 1656.803742 0.000321534 0.011571566 hsa-miR-3158-5p 4975.696087 0.0032277898 0.040466778 hsa-miR-3158-5p 4975.696087 0.0032		hsa-miR-3605-5p		133.0942992	0.01136760	9 0.098199861
hsa-miR-320-5p 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 660.7225572 0.000197999 0.011571566 hsa-miR-342-3p 1101.715332 0.006701458 0.085383056 hsa-miR-4383-5p 3056.692927 0.001919366 0.030134053 hsa-miR-133-3p 59657.02312 0.00189316 0.030134053 hsa-miR-143-3p 59657.02312 0.00189316 0.001571566 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-1550b-3p 1073.589544 0.000368521 0.011571566 hsa-miR-520-3p 1656.803742 0.000321534 0.011571566 hsa-miR-155-5p 5424.877172 0.000614626 0.011571566 hsa-miR-3158-5p 4995.640688 0.003321534 0.011571566 hsa-miR-3158-5p 4995.640688 0.00321534 0.011571566 hsa-miR-3158-5p 4995.640688 0.00321		hsa-miR-15a-5p		3116.809603	0.00154171	5 0.026894357
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 0.01571566 hsa-miR-342-3p 1101.715332 0.008701458 0.085383056 hsa-miR-342-3p 3056.692927 0.0011919366 0.030134053 hsa-miR-100-5p 19870.20135 0.002218999 0.033179315 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-50b-3p 1073.589544 0.000360521 0.019294207 hsa-miR-50b-3p 1656.803742 0.000321534 0.011571566 hsa-miR-50b-3p 1073.589544 0.000321534 0.011571566 hsa-miR-3158-5p 4995.640688 0.003362776 0.040466778 hsa-miR-3158-5p 2018.924614 1.888-05 0.0		hsa-miR-98-5p		4507.765982	0.00112974	6 0.022127632
has-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-342-3p 1001.715332 0.001919366 0.030134053 hsa-miR-100-5p 19870.20135 0.002218999 0.031379315 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-144-5p 2848.681108 0.000860251 0.019294207 hsa-miR-103a-3p 23271.45364 0.000368521 0.019294207 hsa-miR-550b-3p 1073.589544 0.010542922 0.094585073 hsa-miR-502-3p 1656.803742 0.000321534 0.011571566 hsa-miR-3158-3p 4995.640688 0.003362776 0.040466778 hsa-miR-3158-3p 4995.640688 0.003362776 0.040466778 hsa-miR-3158-5p 2018.924614 1.888E-05		hsa-miR-3200-5p		188.938684	0.00119799	3 0.022127632
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 0.031179315 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-143-3p 59657.02312 0.00189316 0.0006140183 hsa-miR-143-3p 59657.02312 0.00189316 0.0006140183 hsa-miR-144-5p 23271.45364 0.000368521 0.011571566 hsa-miR-50b-3p 1073.589544 0.000360251 0.011571566 hsa-miR-50c-3p 1656.803742 0.000321534 0.011571566 hsa-miR-50c-3p 1656.803742 0.000321534 0.011571566 hsa-miR-5158-5p 5424.877172 0.000614626 0.014066778 hsa-miR-3158-5p 2018.924614 1.88E-05 0.002460488 hsa-miR-3158-5p 2018.924614 1.88E-05 0.00		hsa-miR-185-3p		451.4076618	0.00458700	7 0.049666218
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 0.03179315 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-105a-3p 2848.681108 0.000368521 0.011571566 hsa-miR-150b-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-3150-5p 2018.924614 1.88E-05 <td< td=""><td></td><td>hsa-miR-375</td><td></td><td>18727.50688</td><td>0.00284200</td><td>2 0.040466778</td></td<>		hsa-miR-375		18727.50688	0.00284200	2 0.040466778
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-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-103a-3p 23271.45364 0.000368521 0.011571566 hsa-miR-50b-3p 1073.589544 0.010542922 0.094585073 hsa-miR-502-3p 1656.803742 0.000361534 0.011571566 hsa-miR-550b-3p 1073.589544 0.010542922 0.094585073 hsa-miR-5502-3p 1656.803742 0.000321534 0.011571566 hsa-miR-15b-5p 5424.877172 0.000614626 0.010682712 hsa-miR-3158-3p 4995.640688 0.003362776 0.040466778 hsa-miR-3158-5p 2018.924614 1.88E-05 0.002946048 hsa-miR-3161-5p 2018.924614 1.88E-05 0.002946048 hsa-miR-335-5p 895.4888086 0.003385672 0.0		hsa-miR-16-5p		54221.41396	0.00024244	6 0.011571566
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-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-143-3p 59657.02312 0.00189316 0.030134053 hsa-miR-143-5p 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-3158-5p 5424.877172 0.000614626 0.016082712 hsa-miR-3158-3p 4995.640688 0.003362776 0.040466778 hsa-miR-3158-5p 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 0.0		hsa-miR-130b-3p		680.7225572	0.00015979	9 0.011571566
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-50b-3p 1073.589544 0.010542922 0.094585073 hsa-miR-502-3p 1656.803742 0.000321534 0.011571566 hsa-miR-502-3p 1656.803742 0.000321534 0.011571566 hsa-miR-3158-5p 5424.877172 0.000614626 0.016082712 hsa-miR-3158-5p 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-361-5p 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.		hsa-miR-342-3p		1101.715332	0.00870145	8 0.085383056
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-3655p 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-652-3p		3056.692927	0.00191936	6 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 0.000614626 0.016082712 hsa-miR-15b-5p 5424.877172 0.000614626 0.040466778 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-361-5p 895.4888086 0.003385672 0.040466778 hsa-miR-335-5p 895.4888086 0.003385672 0.040466778 hsa-miR-30a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-100-5p		19870.20135	0.00221899	9 0.033179315
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 0.0032277898 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-143-3p		59657.02312	0.0018931	6 0.030134053
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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-103a-3p		23271.45364	0.00036852	1 0.011571566
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 0.003227898 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 ep hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415	\star	hsa-miR-144-5p		2848.681108	0.00086025	1 0.019294207
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 ep hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-550b-3p		1073.589544	0.01054292	2 0.094585073
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-502-3p		1656.803742	0.00032153	4 0.011571566
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-15b-5p		5424.877172	0.00061462	6 0.016082712
hsa-miR-361-5p 2018.924614 1.88E-05 0.002946048 hsa-miR-106b-5p 4725.310902 0.009131329 0.086885981 ep hsa-miR-335-5p 895.4888086 0.003385672 0.040466778 hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-3158-3p		4995.640688	0.00336277	6 0.040466778
hsa-miR-106b-5p 4725.310902 0.009131329 0.086885981 ep hsa-miR-335-5p 895.4888086 0.003385672 0.040466778 hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-3158-5p		4975.696087	0.00327789	8 0.040466778
ep hsa-miR-335-5p 895.4888086 0.003385672 0.040466778 hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-361-5p		2018.924614	1.88E-0	5 0.002946048
ep hsa-miR-500a-3p 1372.329815 0.005452066 0.05522415		hsa-miR-106b-5p		4725.310902	0.00913132	9 0.086885981
	n			895.4888086	0.00338567	2 0.040466778
hsa-miR-1228-5p 349.0790112 0.000474787 0.013553002	-1			1372.329815	0.00545206	6 0.05522415
		hsa-miR-1228-5p		349.0790112	0.00047478	7 0.013553002

Just et al. 2017 In prep

DE miRNAs: Overrepresentation AARHUS UNIVERSITY analysis (pathways)

Category	Subcategory	Enrichment	p-value	expected	observed
Pathways (mIRWalk)	WP51 Regulation of Actin Cytoskeleton	★ over-represented	3.285999-06	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 cyl signaling pathway	tokine over-represented	1.27585e-05	10507	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	X 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	1.84885e-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 G 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	10.0599	22
Pathways (mIRWalk)	WP2018 RANKL RANK Signaling Pathway	over-represented	5.29453e-05	7.43313	19
Pathways (mIRWalk)	WP231 TNF alpha Signaling Pathway	The over-represented	5.61775e-05	8.32735	20
Pathways (miRWalk)	hsa04144 Endocytosis	over-represented	5.61775e-05	11.1776	23
Pathways (miRWalk)	P00035 Interferon gamma signaling pathway	Transformation of the second s	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 re-		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	8.007199-05	6.93014	18
Pathways (miRWalk)	WP366 TGF beta Signaling Pathway1	Transformed and the second sec	8.40145e-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 0.000125379	2.62675	11 19
Pathways (miRWalk)	WP560 TGF beta Signaling Pathway2	+ over-represented			
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

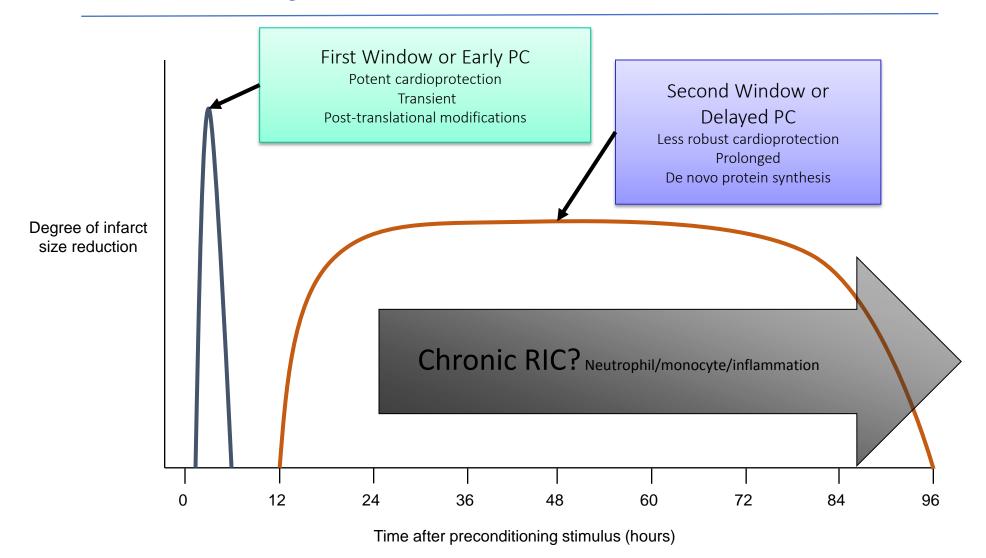
DE miRNAs: OverrepresentationAARHUS UNIVERSITYAARHUS UNIVERSITYDE miRNAs: Overrepresentationanalysis (target genes)

P-value

Number of time observed

	Category 🗘	Subcategory 🗘		Enrichment 🗘	p-value 🛧	expected 🗘	observed 🗘	miRNAs/precursors 🗘		Category 🗘	Subcategory 🗘		Enrichment	p-value 🗘	expected 🗘	observed ~	miRNAs/precursors 🗘
	Target genes (miRTarbase)	PDK4	1	over-represented	0.00894596	0.208633	4	hsa-miR-26b-5p; haa-miR-16-5p; hsa-miR-103a-3p; hsa-miR-335-5p	1	Target genes (miRTarbase)	EEF1A1	1	over-represented	0.0395211	2.19065	7	hsa-miR-23b-3p) haa-miR-26b-5p; haa-miR-16-5p; hsa-miR-652-3p) haa-miR-100-5p;
2	Target genes (miRTarbase)	SMAD7	1	over-represented	0.00894596	0.573741	6	hsa-miR-26b-5p; haa-miR-98-5p;									haa-miR-15b-5p; haa-miR-106b-5p
¥			-					haa-miR-16-5p; haa-miR-100-5p; hsa-miR-103a-3p; haa-miR-15b-5p	2	Target genes (miRTarbase)	VEGPA	1	over-represented	0.0364171	2.13849	7	haa-miR-107; haa-miR- 15a-5p; hsa-miR- 16-5p; hsa-miR- 15b-5p; haa-miR-
3	Target genes (miRTarbase)	TNFSF9	1	over-represented	0.00894596	0.208633	4	hsa-miR-26b-5p) hsa-miR-98-5p) hsa-miR-16-5p) hsa-miR-335-5p	_								361-5p; hsa-miR- 106b-Sp; hsa-miR- 335-5p
4	Target genes (miRTarbase)	CDK17	t	over-represented	0.0129327	0.260791	4	hsa-mik-335-5p hsa-mik-98-5p; haa-mik-16-5p; haa-mik-103a-3p; haa-mik-335-5p	з	Target genes (miRTarbase)	ACTG1	1	over-represented	0.0298026	1,46043	6	hsa-miR-423-50) haa-miR-99b-50; haa-miR-962-30) haa-miR-342-30) haa-miR-361-50
5	Target genes (miRTarbase)	GNS	1	over-represented	0.0129327	0.260791	4	hsa-miR-23b-3p) hsa-miR-107) hsa-miR- 103a-3p) hsa-miR- 335-5p	4	Target genes (miRTarbase)	CCND2	1	over-represented	0.0298026	1.2518	6	hsa-miR-423-5p; hsa-miR-15a-5p; hsa-miR-16-5p; hsa-miR-342-3p;
6	Target genes (miRTarbase)	HSPALA	1	over-represented	0.0129327	0.260791	4	haa-miR-146a-5p; haa-miR-15a-5p;									hsa-miR-106b-5pj hsa-miR-335-5p
	(1111,101,0000)		•					hsa-miR-16-5pj hsa-miR-335-5p	5	Target genes	CONE1	+	over-represented	0.0158562	0.856691	6	has-miR-26b-5p;
7	Target genes (miRTarbase)	PLSCR4	1	over-represented	0.0129327	0.260791	4	haa-miR-16-5p; haa-miR-103a-3p; haa-miR-13b-5p; hsa-miR-335-5p		(miRTarbase)		•					haa-miR-107; haa-miR- 15a-5p; hsa-miR- 16-5p; haa-miR- 103a-3p; haa-miR- 15b-5p
8	Target genes (miRTarbase)	RAD51C	1	over-represented	0.0129327	0.260791	4	hsa-miR-26b-5p) hsa-miR-15a-5p) hsa-miR-16-5p; hsa-miR-100-5p	6	Target genes (miRTarbase)	DICER1	1	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
9	Target genes (miRTarbase)	SHOC2	1	over-represented	0.0129327	0.250791	4	haa-miR-26b-5p; haa-miR-16-5p;	7	Target genes	PLAG1	+	over-represented	0.0158562	0.886691	6	haa-miR-26b-5p;

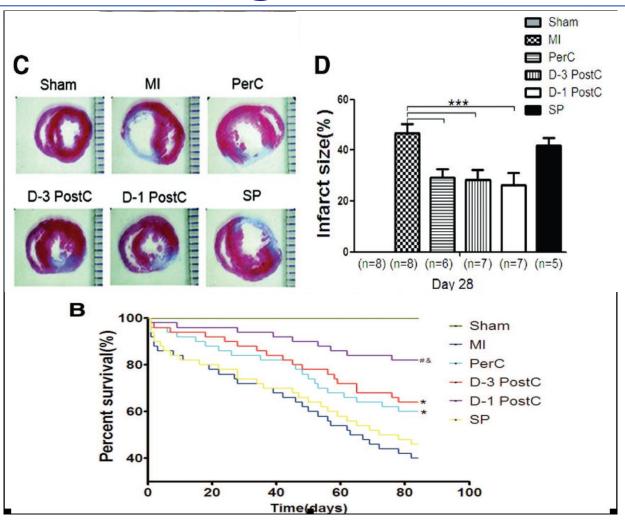
Phases of Protection: Beyond IR Protection?



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?