Training-induced adaptations in the vascular system – can they enhance performance?

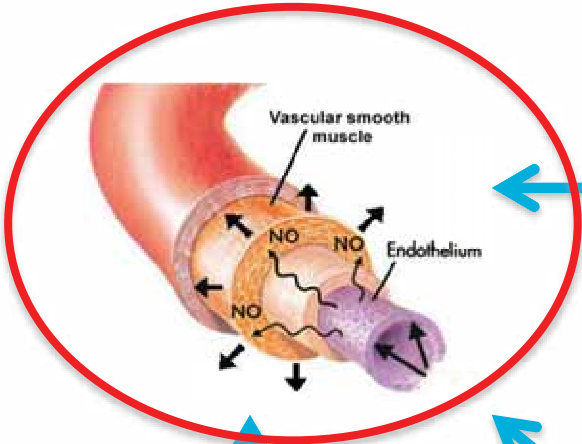
Tim Cable

Department of Sports Science

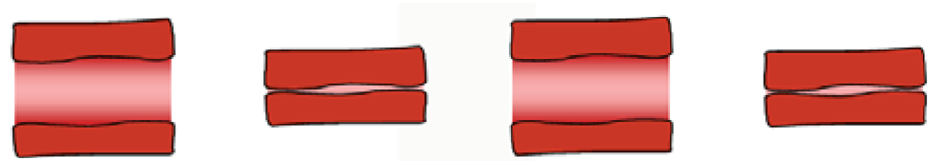
ASPIRE ACADEMY

inspired by aspire®

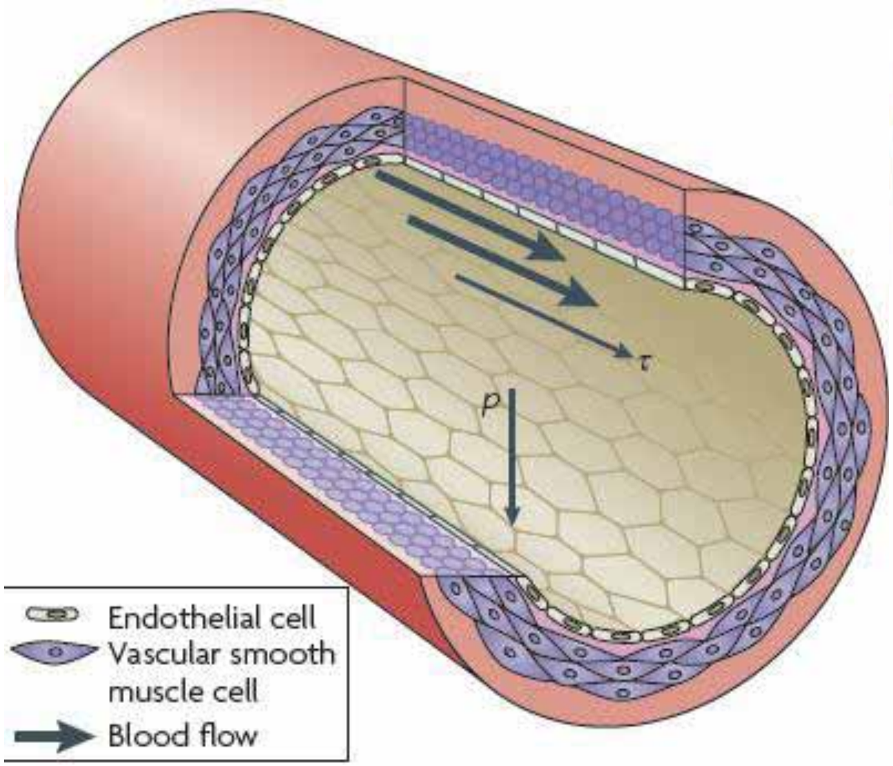
Plan

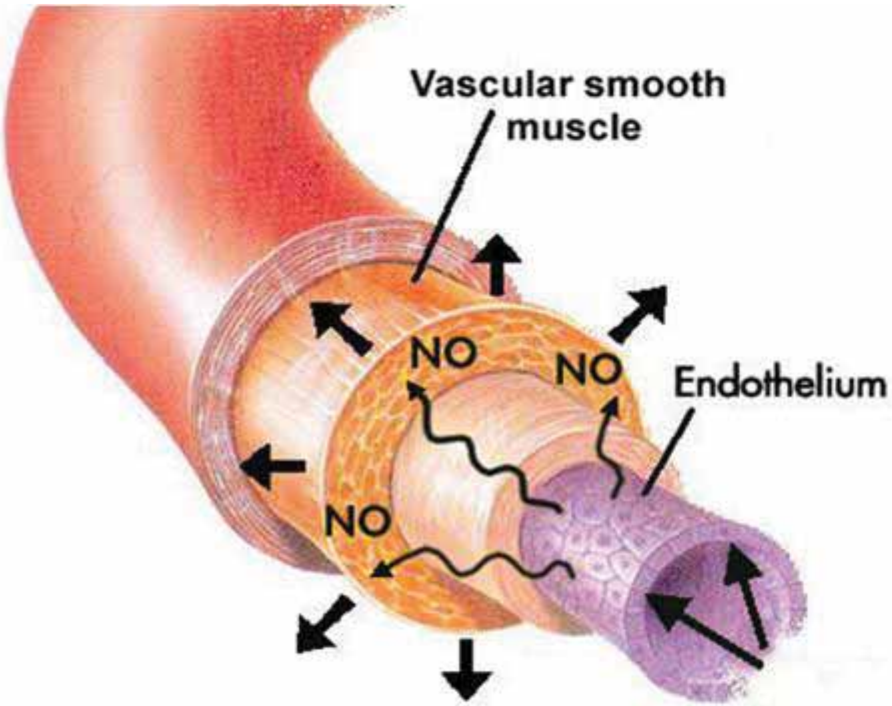


Ischemic preconditioning (3/4 x 5 min)



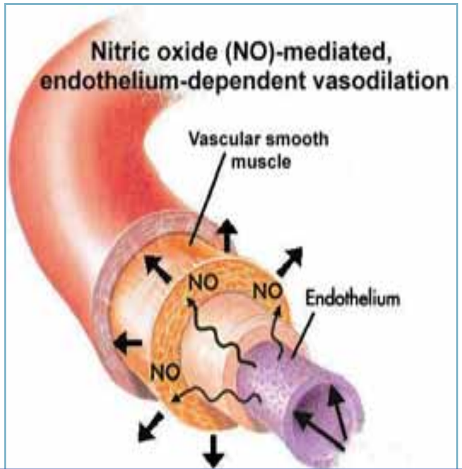
Endothelial stimulus: Shear Stress

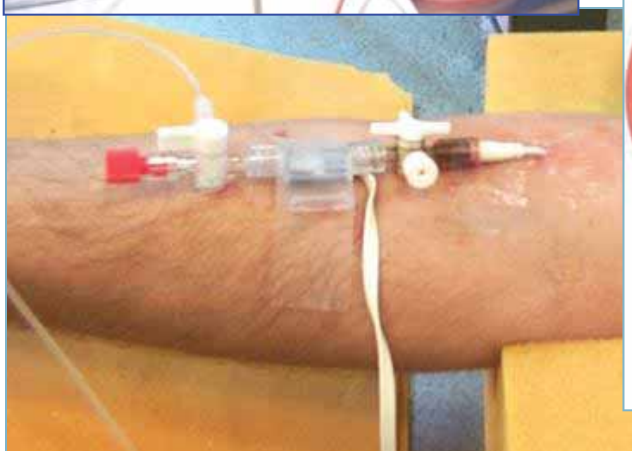


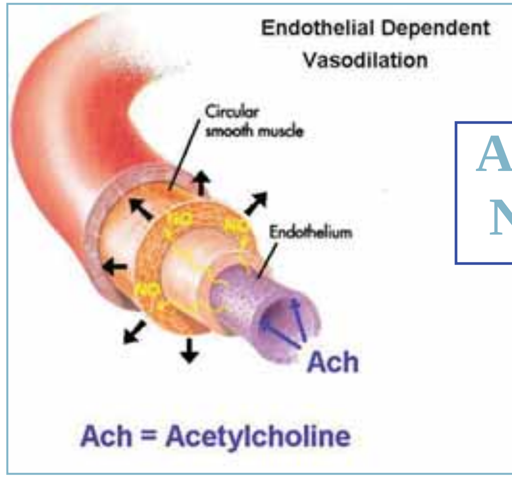


Acute increases in shear stress enhance endothelial function

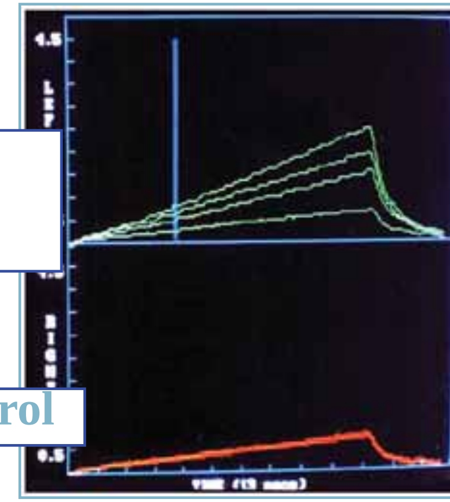
Plethysmography





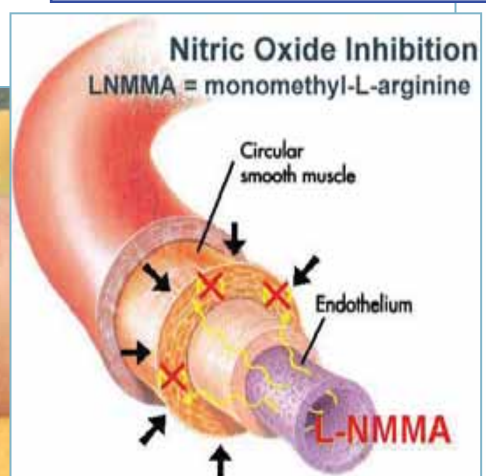


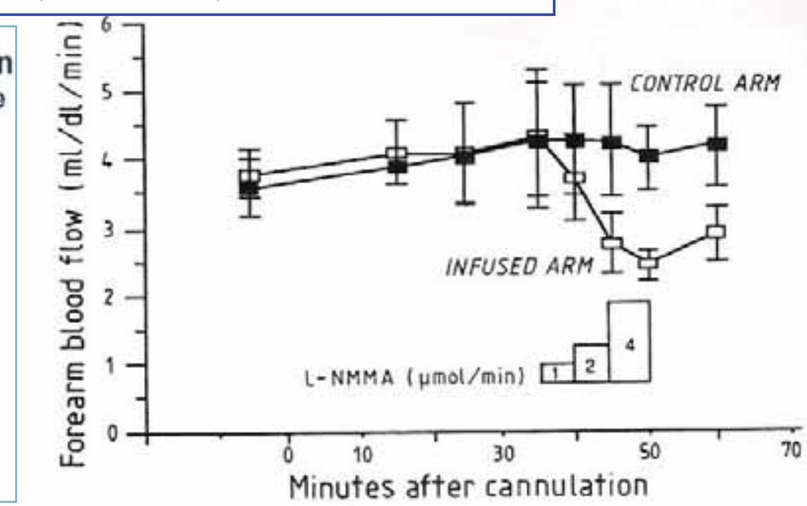
ACh infusion
NO ↑↑



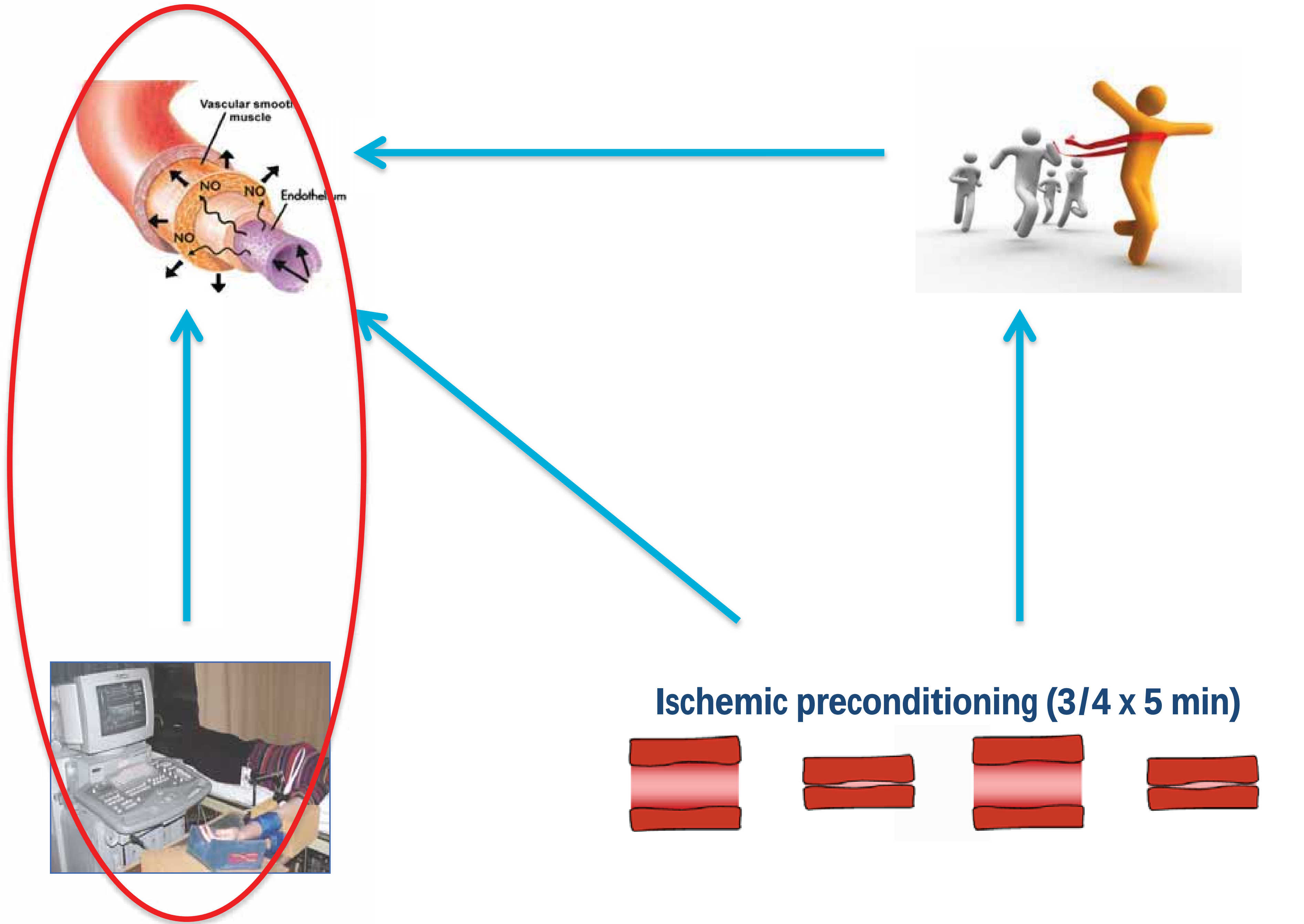
Saline control

LNMMA infusion (NO↓↓)





Plan

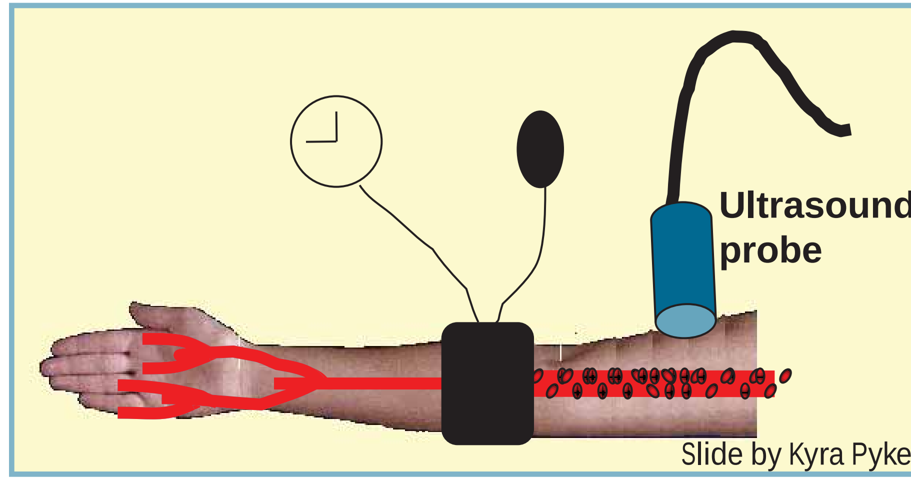

Vascular smooth
muscle
NO
NO
NO
Ischemic preconditioning (3/4 x 5 min)

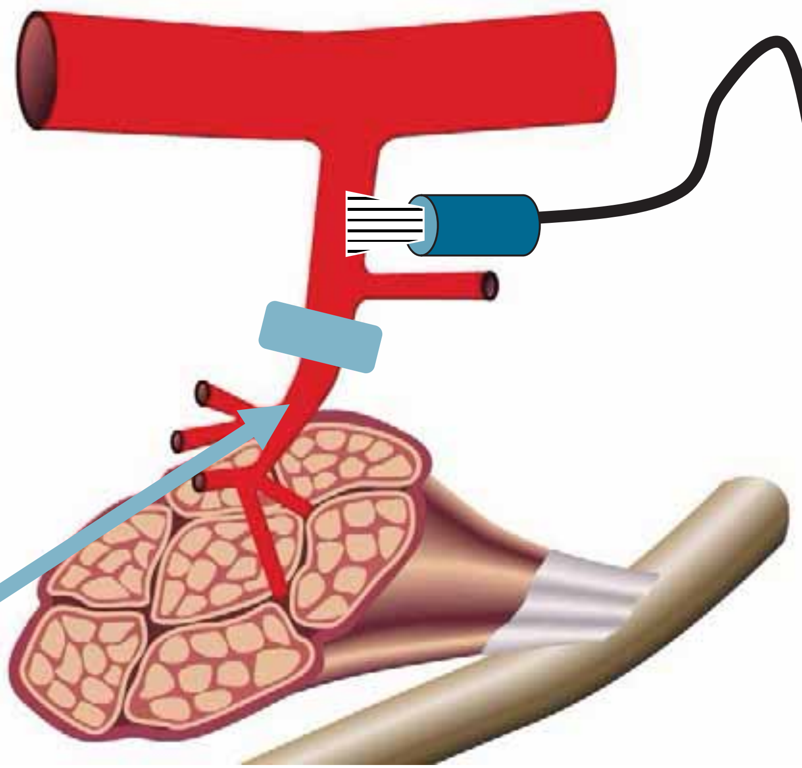
Flow-mediated dilation (FMD)

Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis

DAVID S. CELERMAJER KELD E. SORENSEN VANDA M. GOOCH
DAVID J. SPIEGELHALTER OWEN I. MILLER IAN D. SULLIVAN
JUNE K. LLOYD JOHN E. DEANFIELD

Lancet 1992; **340**: 1111–15.

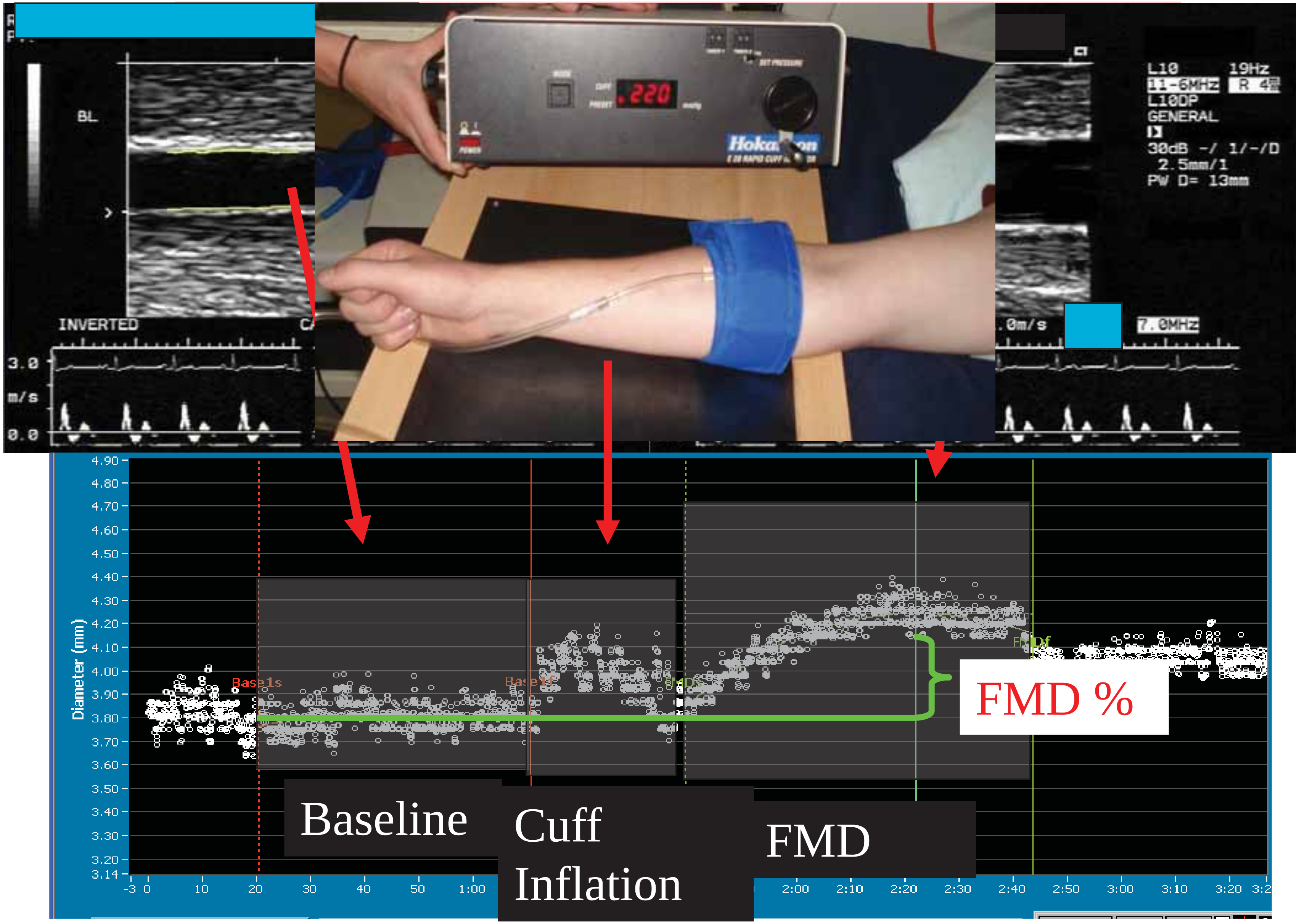




Occluding cuff ~220 mmHg

Vascular Function

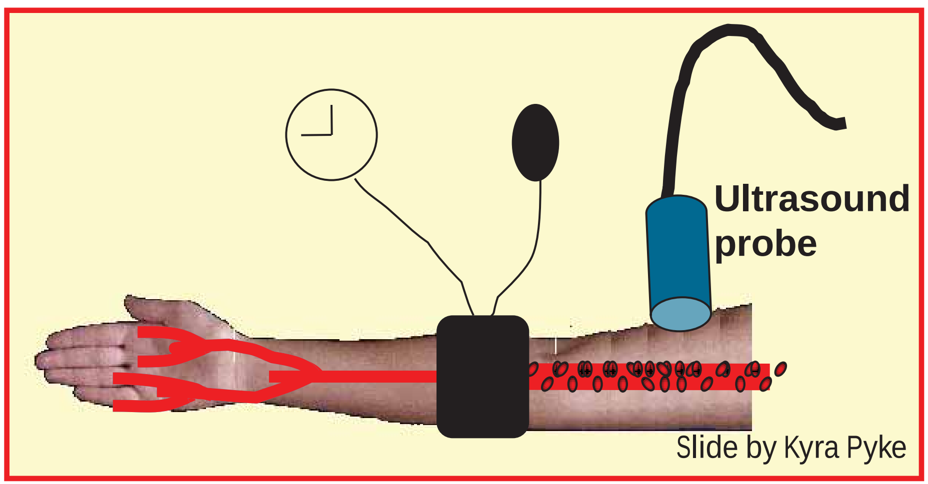
Flow-mediated dilation (FMD)

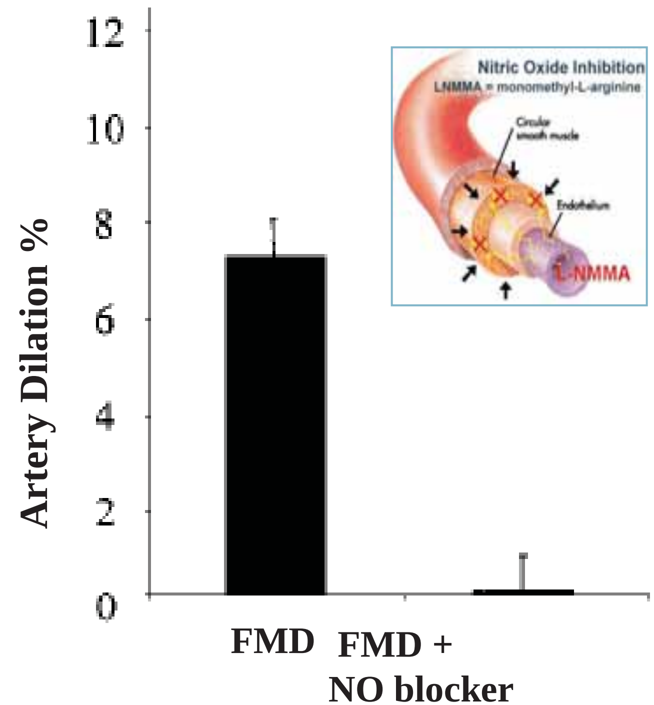


Macrovascular Assessment

Endothelial function: NO-dependent measure

Flow mediated dilation (FMD)





Doshi et al. Clinical Science 2001

FMD:
Endothelial function: NO-dependent measure

Relationship between coronary and peripheral conduit artery function: Pharmacological and physiological NO-mediated stimuli

Endothelium-Dependent Flow-Mediated Vasodilation in Coronary and Brachial Arteries in Suspected Coronary Artery Disease

Bonpei Takase, MD, Akimi Uehata, MD, Takashi Akima, MD, Tomoo Nagai, MD, Toshihiko Nishioka, MD, Akira Hamabe, MD, Kimio Satomura, MD, Fumitaka Ohsuzu, MD, and Akira Kurita, MD

Close relationship between the vasodilator response to acetylcholine in the brachial and coronary artery in suspected coronary artery disease

Bonpei Takase[a,*], Akira Hamabe[a], Kimio Satomura[b], Takasi Akima[a], Akimi Uehata[a], Fumitaka Ohsuzu[b], Masayuki Ishihara[a], Akira Kurita[a]

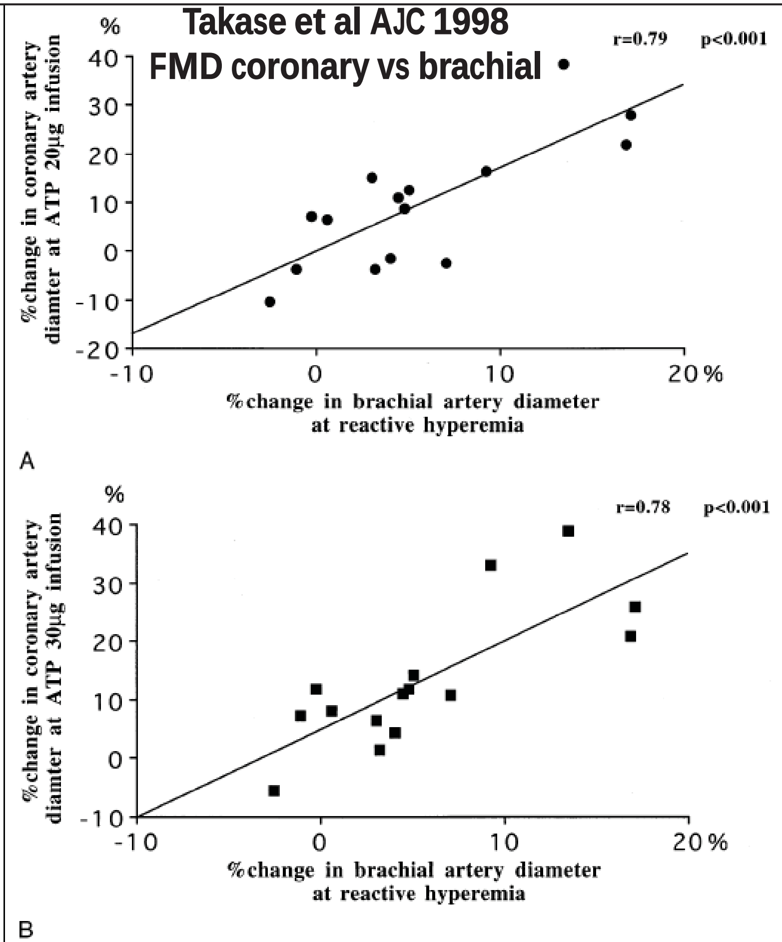
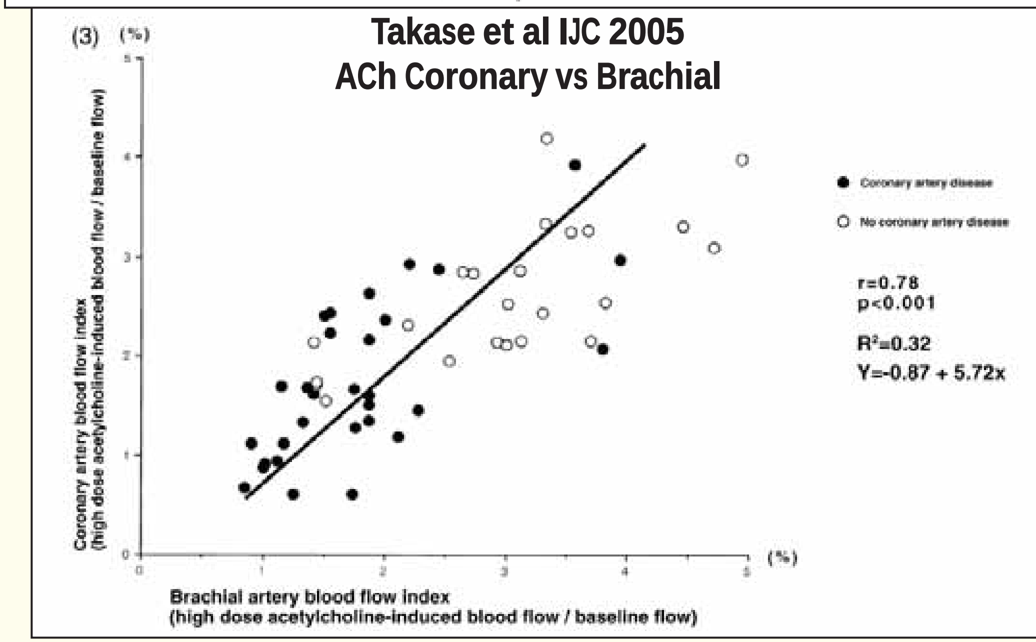


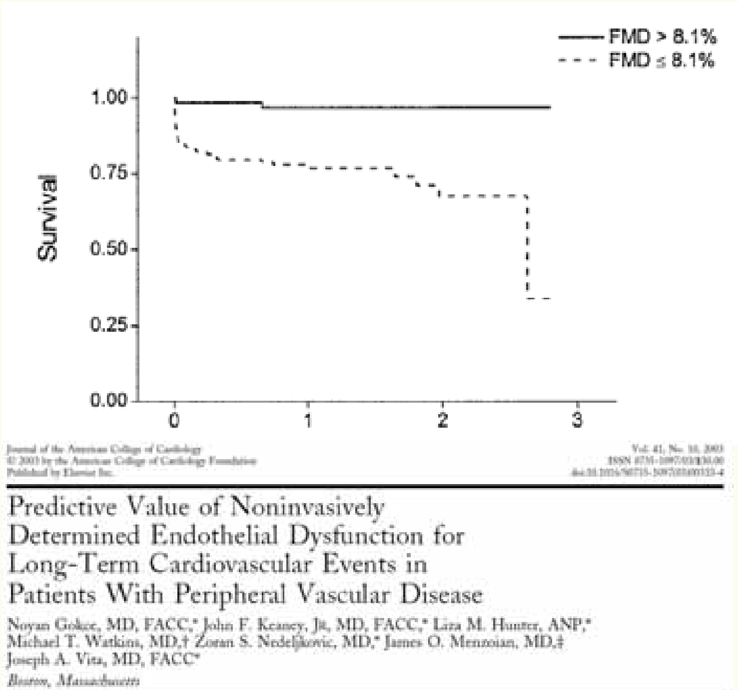
FIGURE 1. *A*, relation between flow-mediated dilation in a coronary artery stimulated by 20 μg of ATP and flow-mediated dilation in a brachial artery stimulated by hyperemia (r = 0.79, p <0.001). *B*, relation between flow-mediated dilation in a coronary artery stimulated by 30 μg of ATP and flow-mediated dilation in a brachial artery stimulated by hyperemia (r = 0.78, p <0.001).

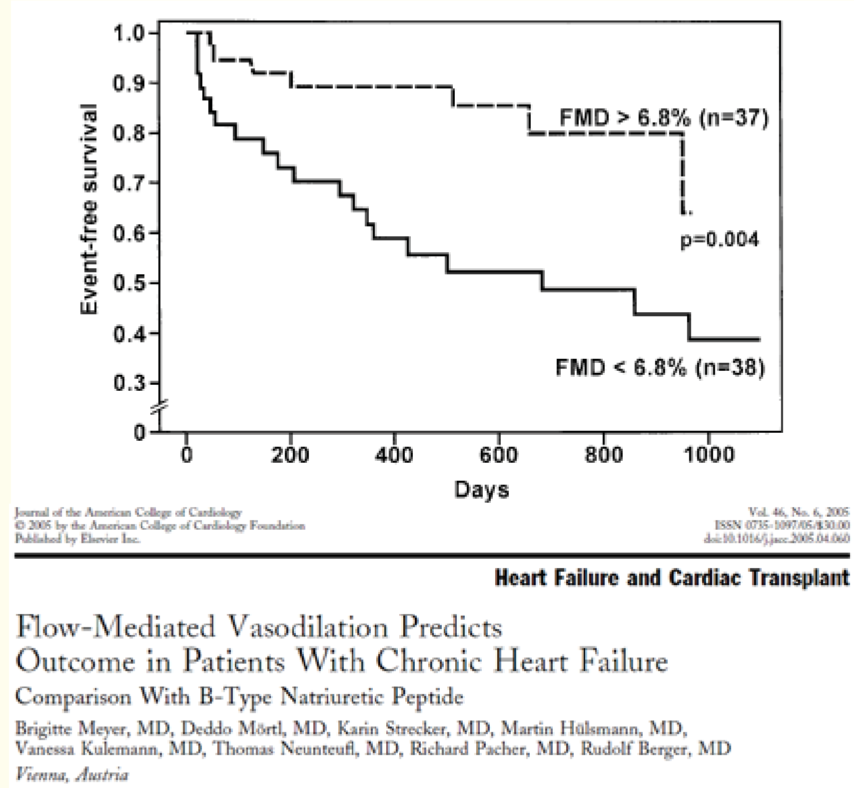


Like-for-like comparisons:

- Coronary vs Brachial:
  - FMD r = 0.79
  - ACh r = 0.78

Does FMD predict prognosis in those at high risk?





- ***10 Studies of FMD and cardiac events/outcomes:***
  - ***ACS (1 n=98), CAD (2, n=444, 106), Chest pain (2; n=398, 73), CHF (2; n=75, 67), PVD (2; n=199, 131), hypertens (1, n=400)***

FMD strongest independent predictor (8/10)

Does FMD identify asymptomatics at high risk in future?

Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease ☆

International Journal of Cardiology 134 (2009) 52 – 58

Michael Shechter [a,b,*], Assaf Issachar [a,b], Ibrahim Marai [a,b], Nira Koren-Morag [a,b], Dov Freinark [a,b], Yael Shahar [a,b], Alon Shechter [a,b], and Micha S. Feinberg [a,b]

- 435 healthy subjects
- (65% men)
- 54 yrs
- 48 events, 36 month follow up
- Median FMD best multivariate predictor of events

- ***FMD provides prognostic info additional to risk factors***

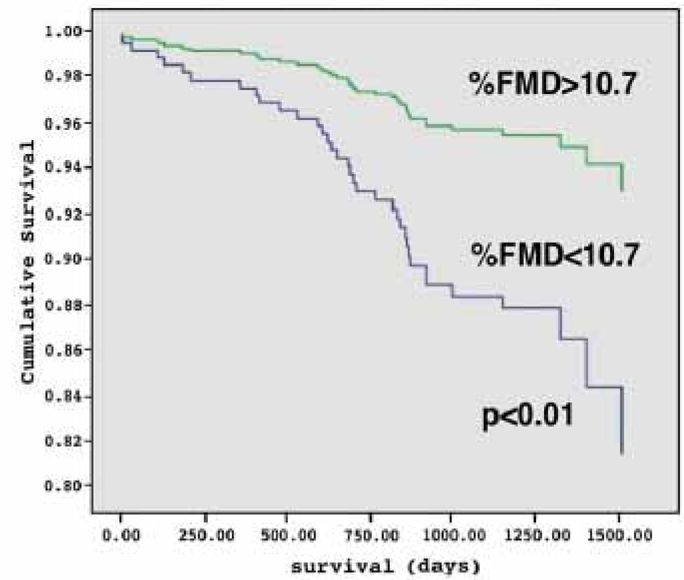
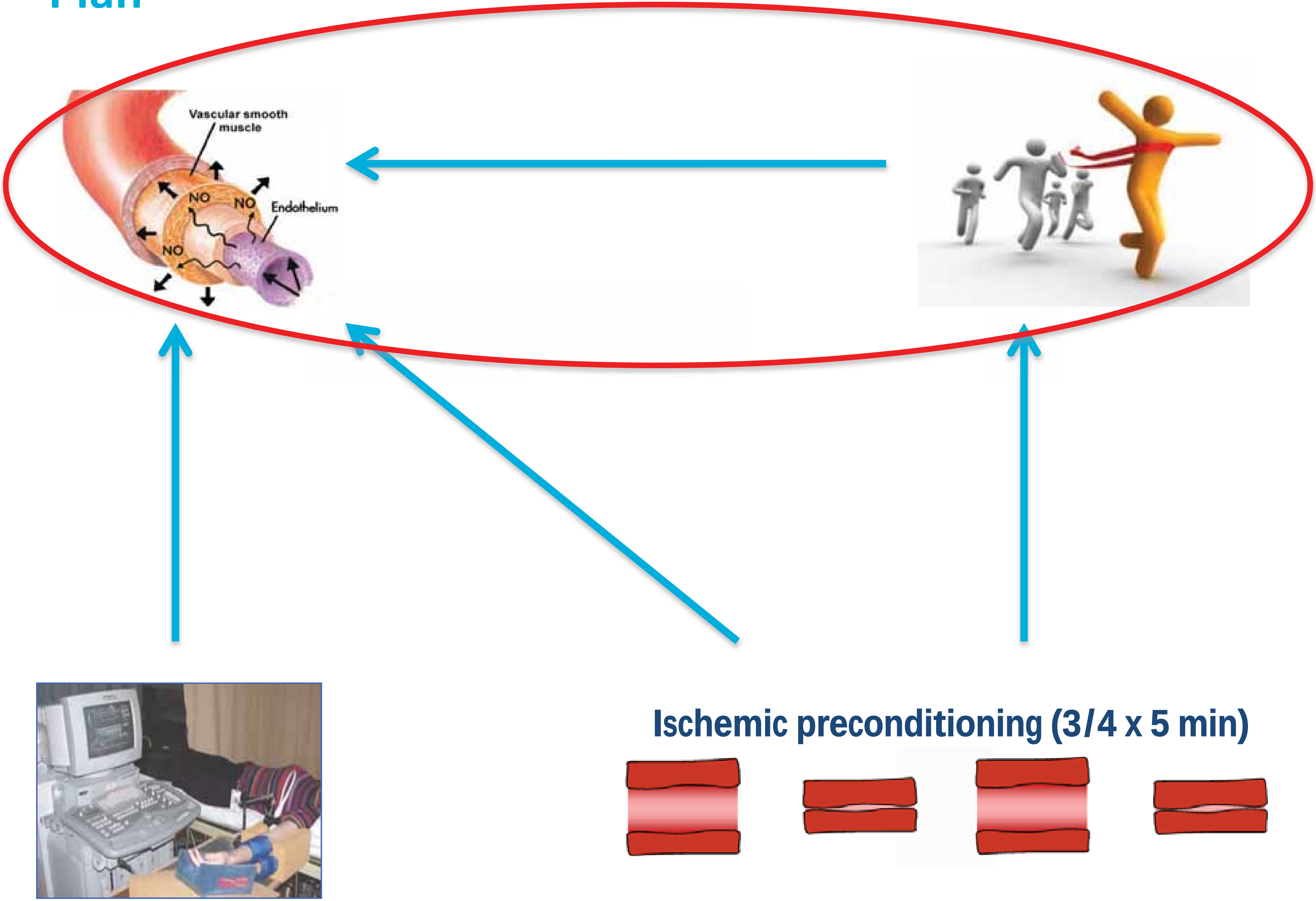


Fig. 1. A Kaplan–Meier survival curve showing survival until first composite adverse cardiovascular endpoint (all-cause mortality, non-fatal myocardial infarction, heart failure or angina pectoris hospitalization, stroke, coronary artery bypass grafting and percutaneous coronary interventions) in subjects with flow-mediated dilation (FMD) above (dashed line) and below (solid line) median value of 10.7%, after controlling for traditional risk factors (age, sex, lipoproteins, diabetes, hypertension, body mass index). Patients with FMD below the median had higher composite adverse cardiovascular endpoints compared to those above the median ($p<0.001$).

Plan


Vascular smooth muscle
NO
NO
NO
Endothelium
Ischemic preconditioning (3/4 x 5 min)

J Appl Physiol 110: 1190–1195, 2011.
First published February 24, 2011; doi:10.1152/japplphysiol.01371.2010.

Exercise and arterial adaptation in humans: uncoupling localized and systemic effects

Nicola J. Rowley,[1] Ellen A. Dawson,[1] Gurpreet K. Birk,[1] N. Timothy Cable,[1] Keith George,[1] Greg Whyte,[1] Dick H. J. Thijssen,[1,2] and Daniel J. Green[1,3]

[1]*Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, United Kingdom;* [2]*Department of Physiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and* [3]*School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, Western Australia, Australia*

Submitted 23 November 2010; accepted in final form 18 February 2011

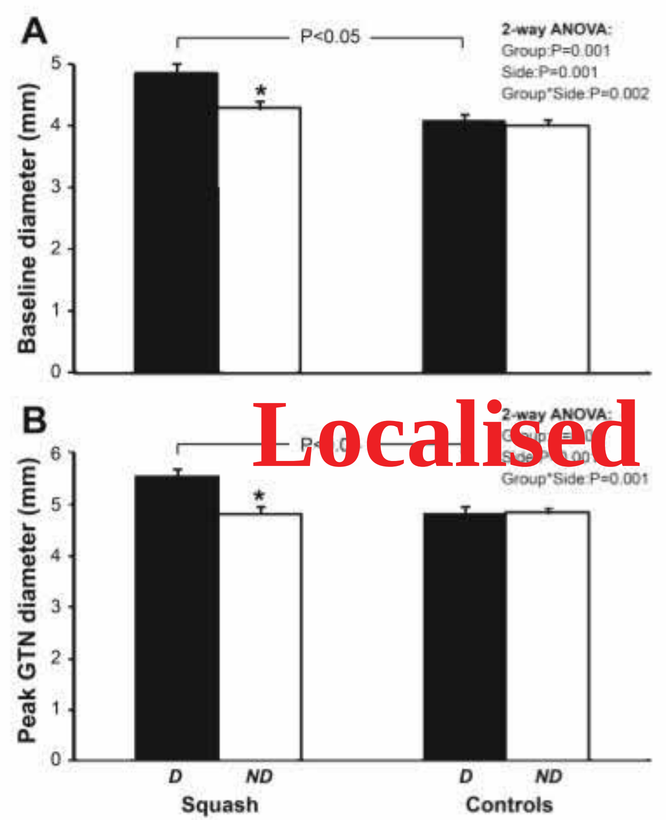


Fig. 1. Brachial artery (BA) baseline (*A*) and peak diameter (*B*) in the dominant (D) and nondominant (ND) side in squash players (n = 13) and controls (n = 16). Values are means ± SE. *Significantly different from the D side at P < 0.05. P value refers to a post hoc unpaired t-test between squash players and controls. Results from the two-way ANOVA are presented. GTN, glyceryl trinitrate.

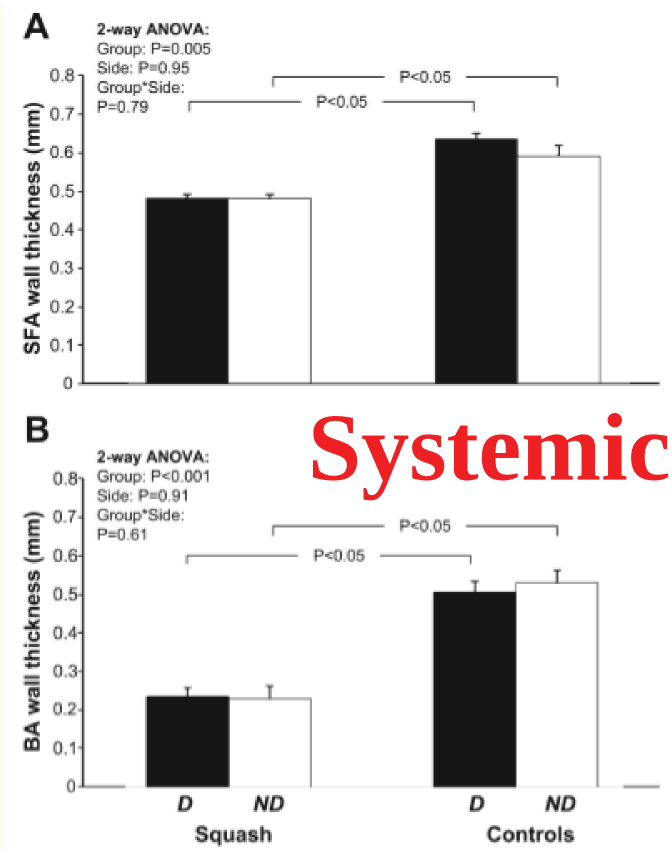


Fig. 2. Superficial femoral artery (SFA; *A*) and BA (*B*) wall thickness in the D and ND side in squash players (n = 13) and controls (n = 16). Values are means ± SE. P value refers to a post hoc unpaired t-test between squash players and controls. Results from the two-way ANOVA are presented.

J Appl Physiol 110: 1190–1195, 2011.
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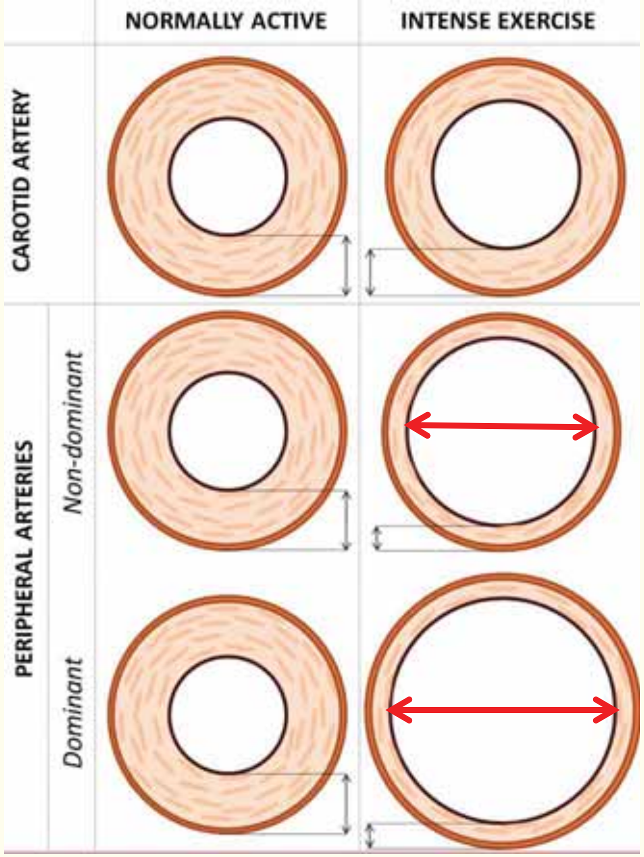
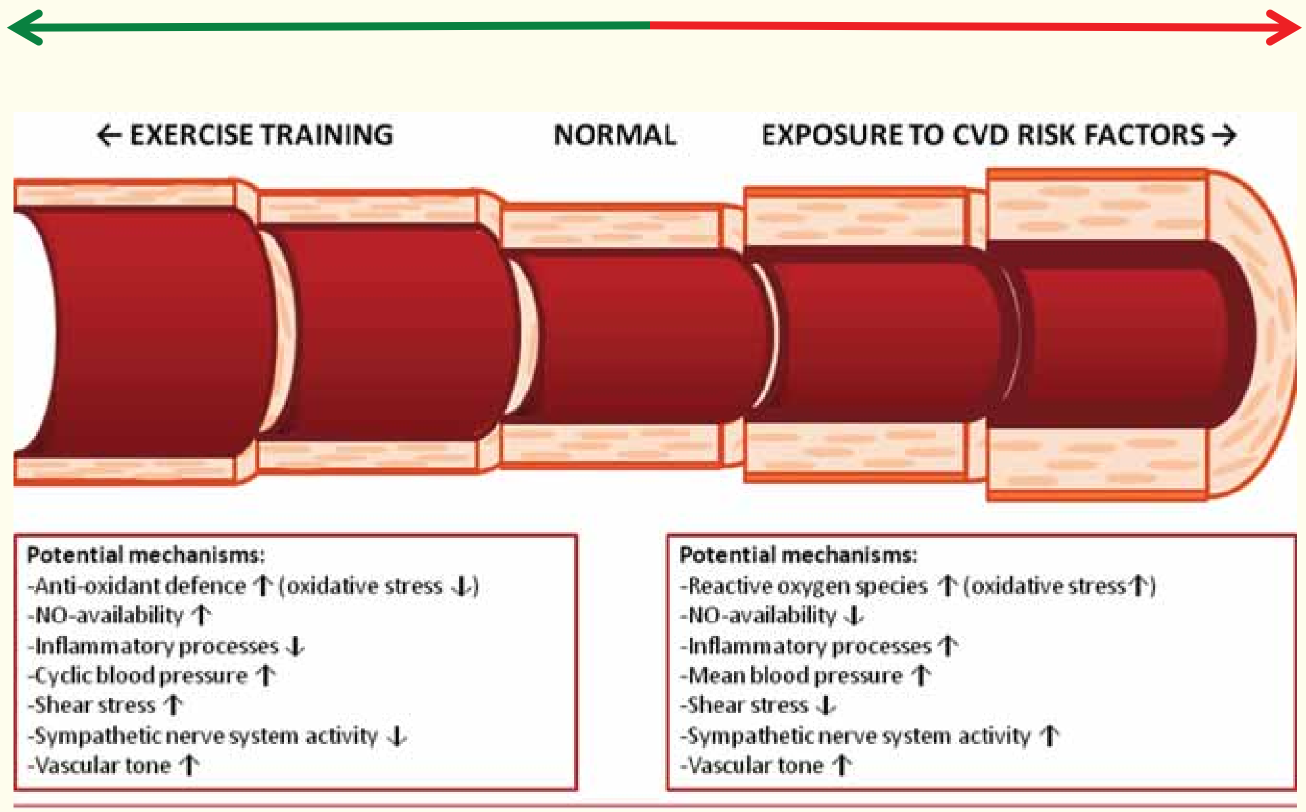


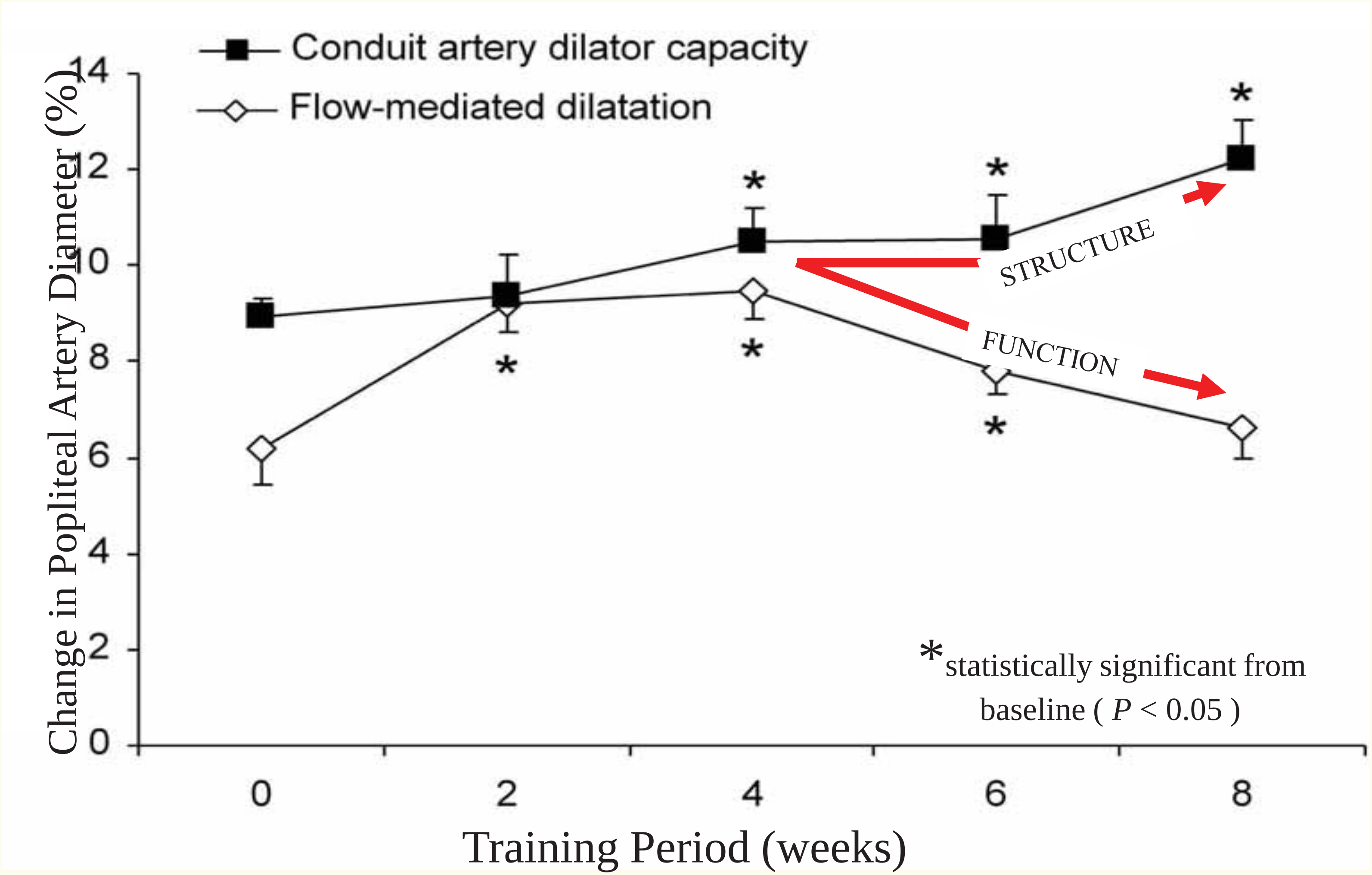
Summary



← EXERCISE TRAINING
NORMAL
EXPOSURE TO CVD RISK FACTORS →
Potential mechanisms:
-Anti-oxidant defence ↑ (oxidative stress ↓)
-NO-availability ↑
-Inflammatory processes ↓
-Cyclic blood pressure ↑
-Shear stress ↑
-Sympathetic nerve system activity ↓
-Vascular tone ↑
Potential mechanisms:
-Reactive oxygen species ↑ (oxidative stress ↑)
-NO-availability ↓
-Inflammatory processes ↑
-Mean blood pressure ↑
-Shear stress ↓
-Sympathetic nerve system activity ↑
-Vascular tone ↑

Popliteal Artery

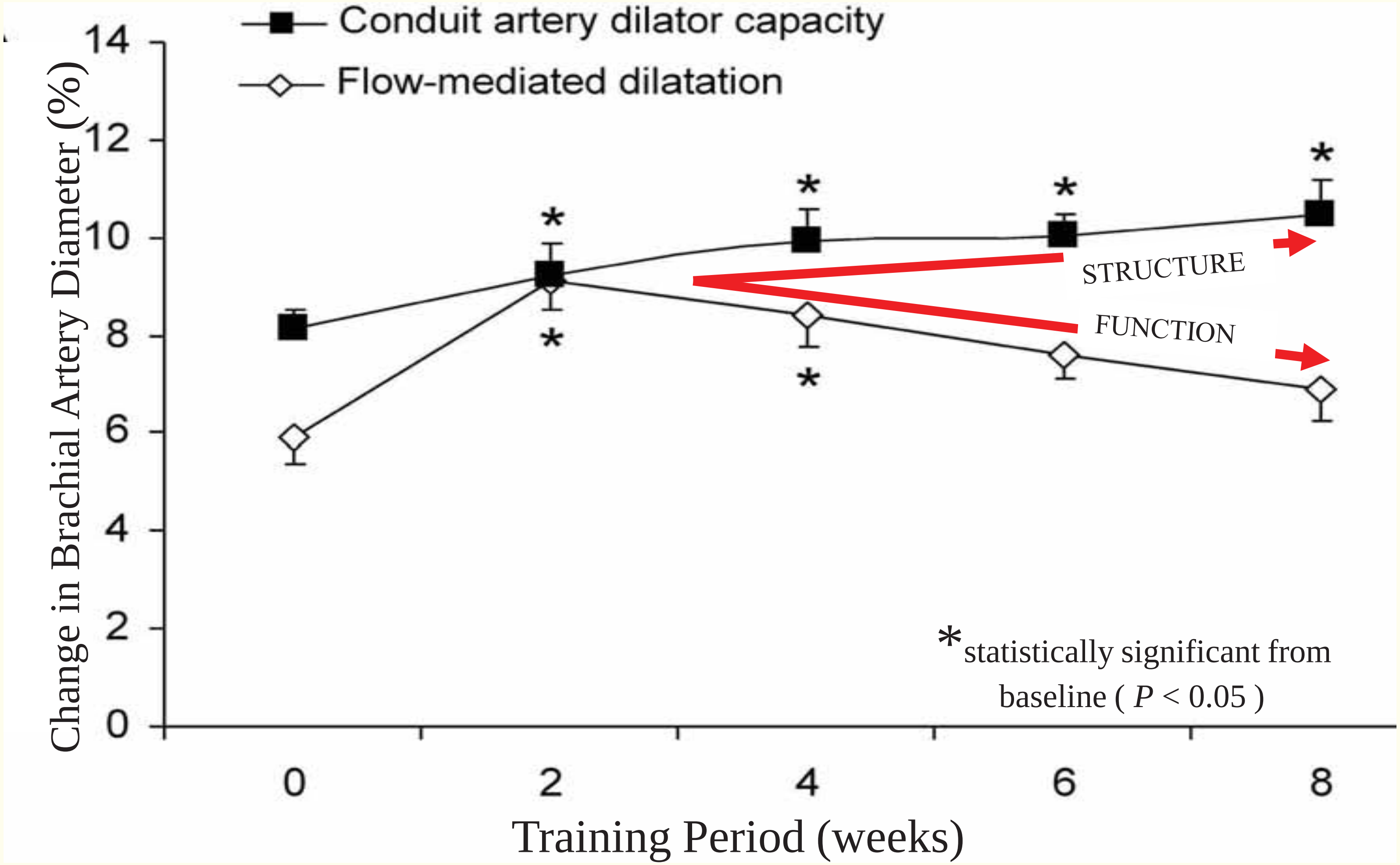
↑Function (FMD) and Structure (CADC)



Tinken et al., J.Physiol, 2008

Brachial Artery

↑ Function (FMD) and Structure (CADC)

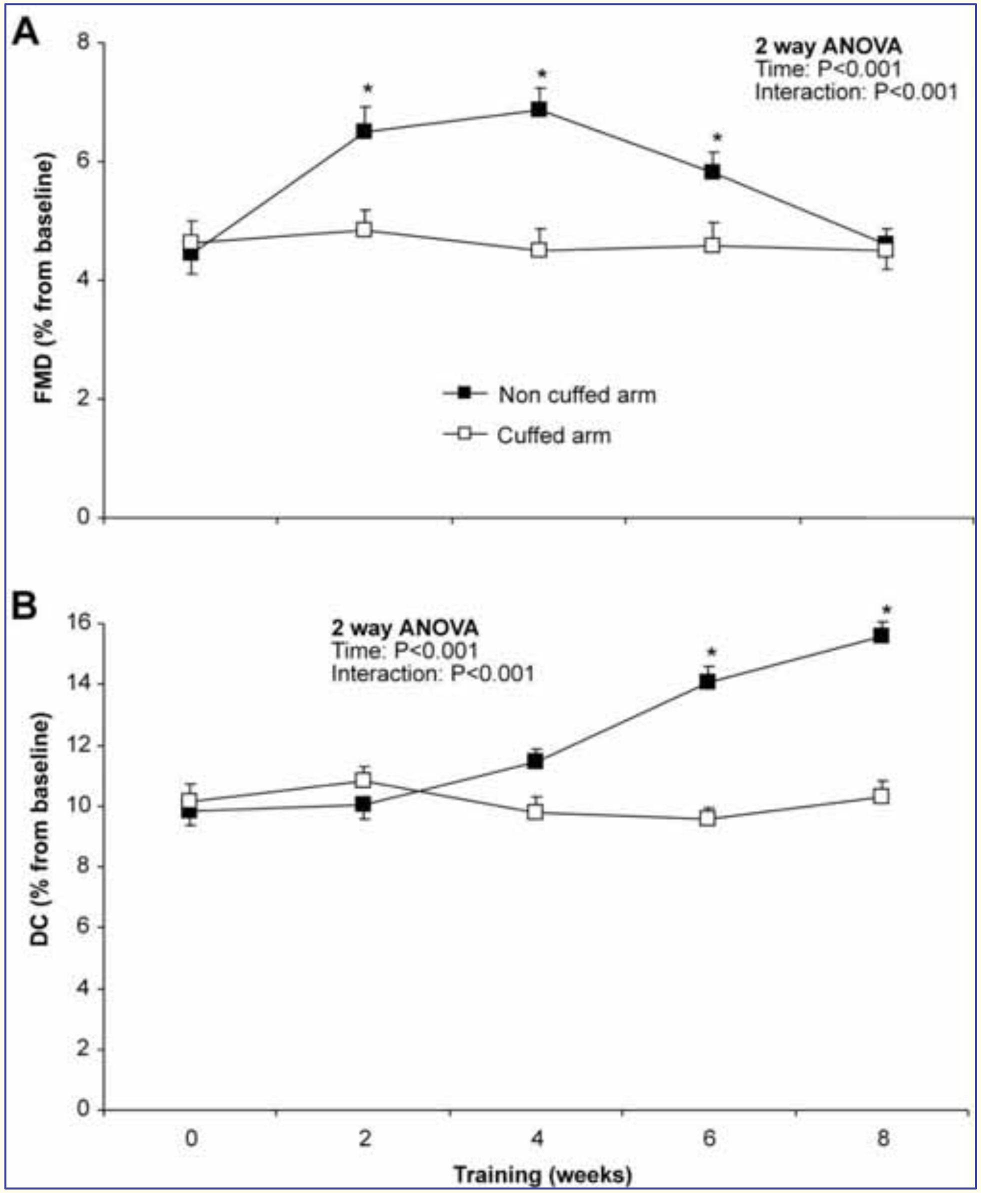


Tinken et al., J.Physiol, 2008

Impact of Handgrip Training:

- Time-course of change in function and structure.

- Impact of cuff placement and shear modulation

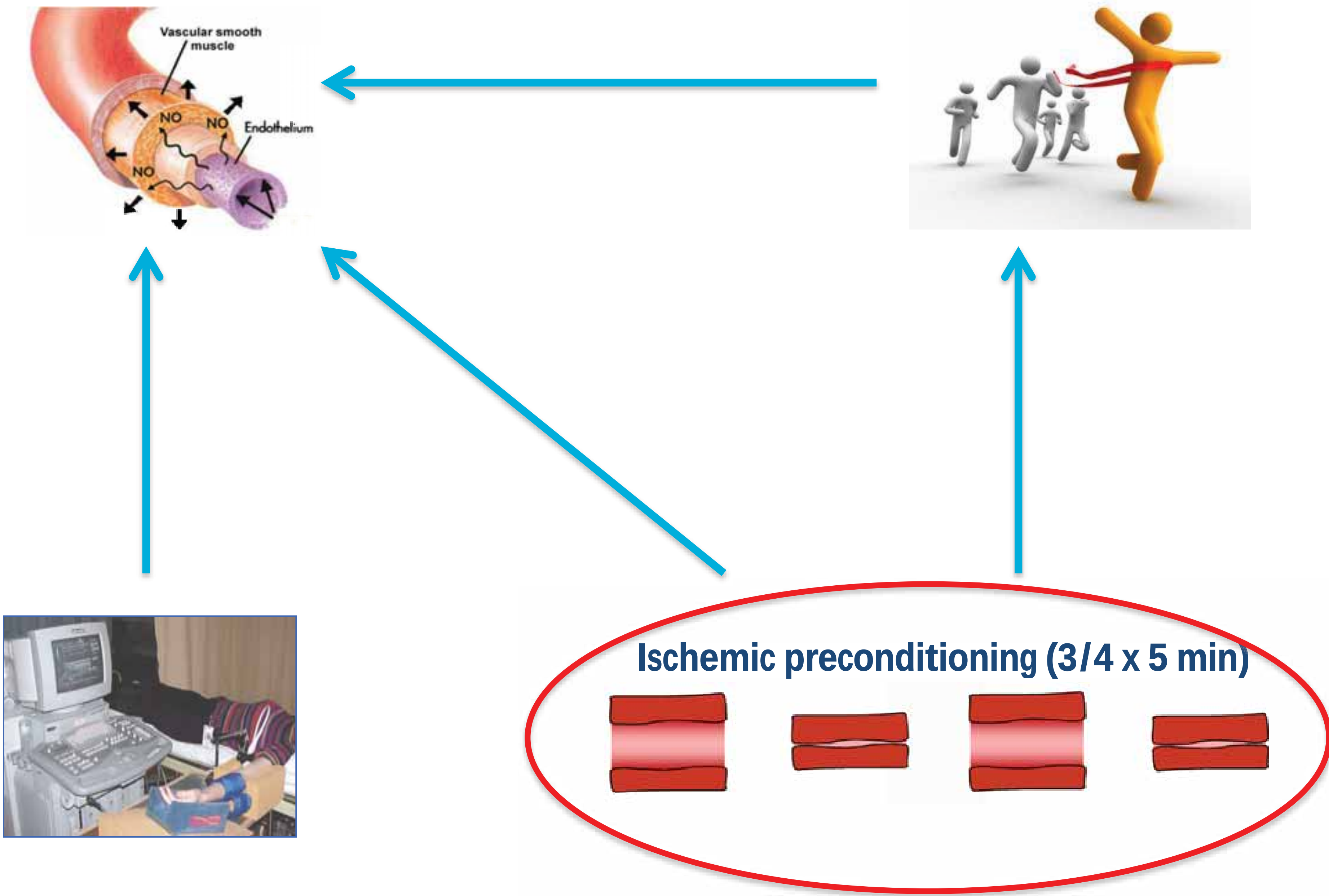


- Handgrip induces localised effects

- Bilateral training induces changes in forearm volume, strength and girth

- ***No change in vascular function or structure if shear is held at baseline levels***

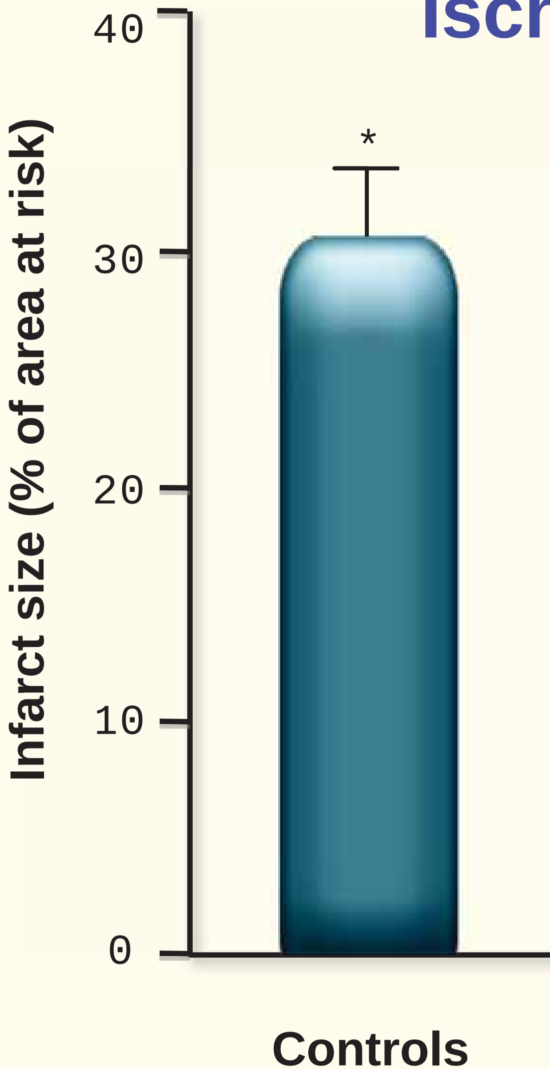
Plan

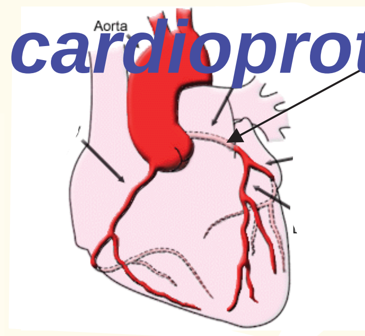

Vascular smooth muscle
NO
NO
NO
Endothelium
Ischemic preconditioning (3/4 x 5 min)

INTRODUCTION

Ischaemic preconditioning: cardioprotective

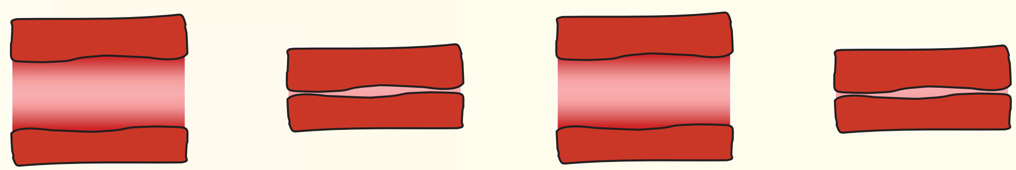
Artificial myocardial infarction (dogs)





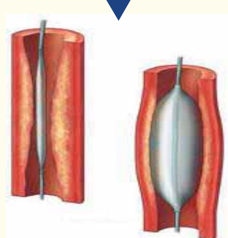
Ligation (40 min)

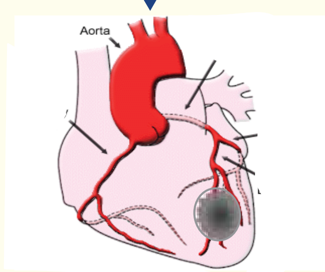
Ischaemic preconditioning (4 X 5 min)



Murry *Circulation* 1986

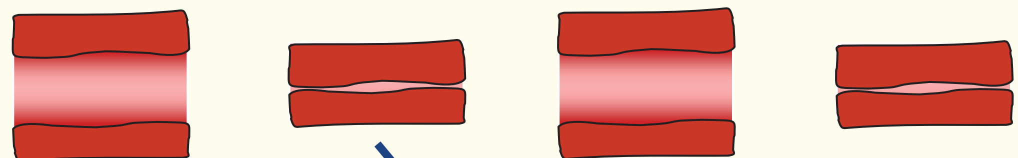
INTRODUCTION

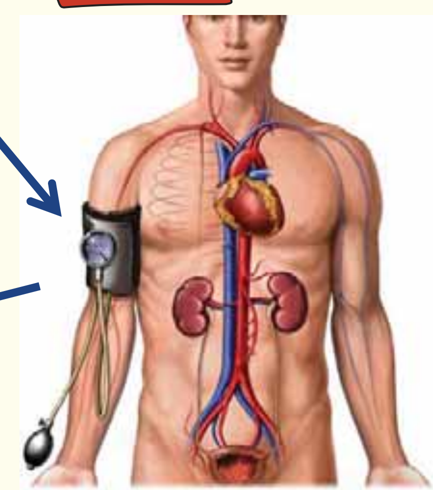




Ischemic preconditioning:
cardioprotective!!!
+
systemic effect!!!

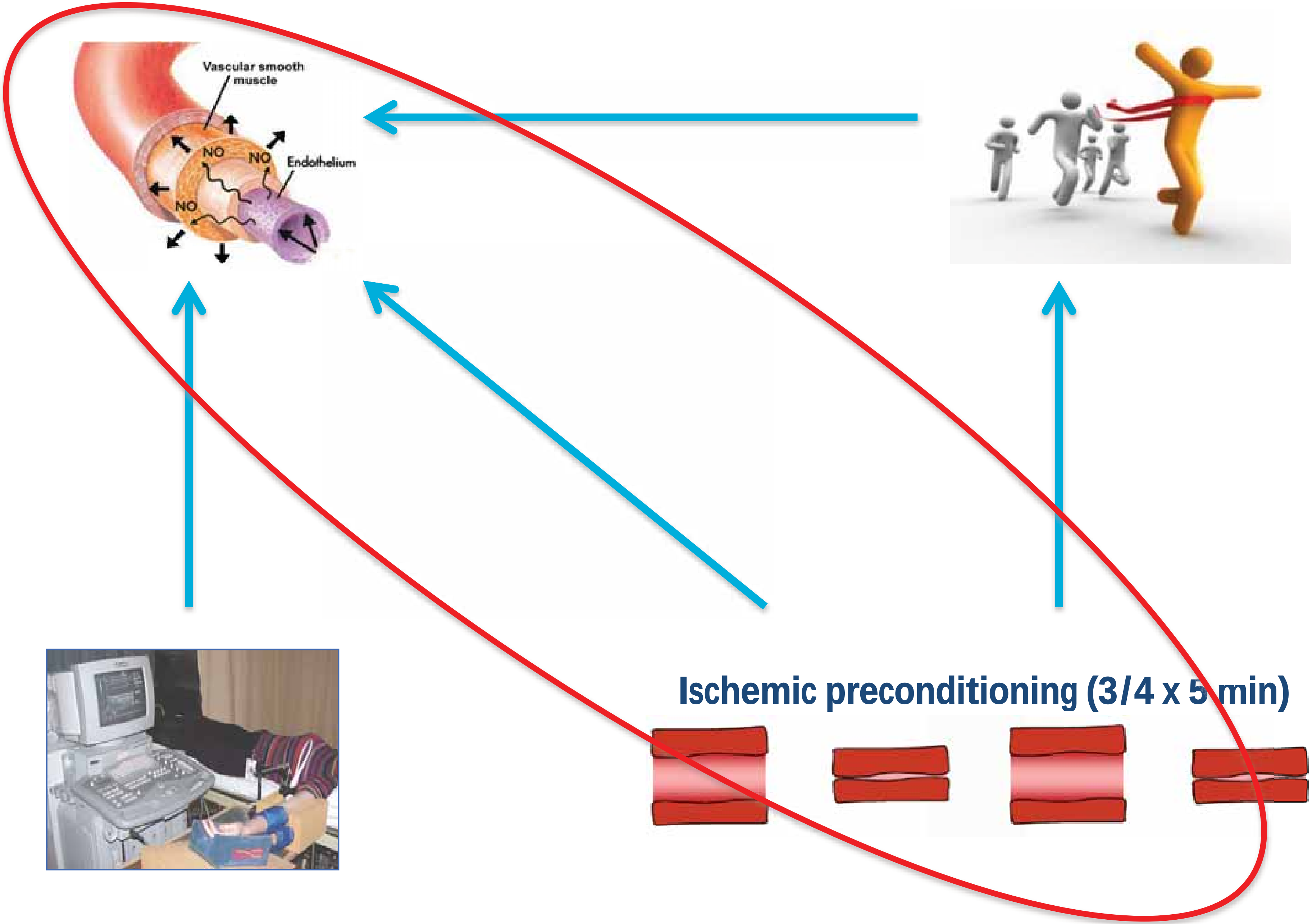
Ischemic preconditioning (4 X 5 min)



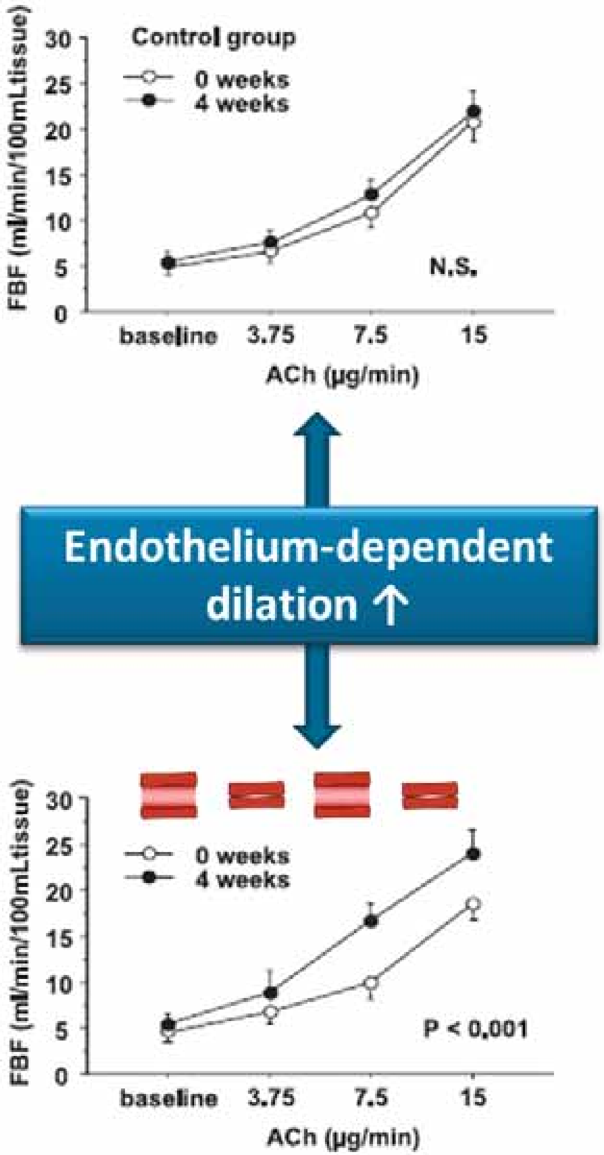


[1]Bøtker, *Lancet*, 2010

Plan


Vascular smooth muscle
NO
NO
NO
Endothelium
Ischemic preconditioning (3/4 x 5 min)

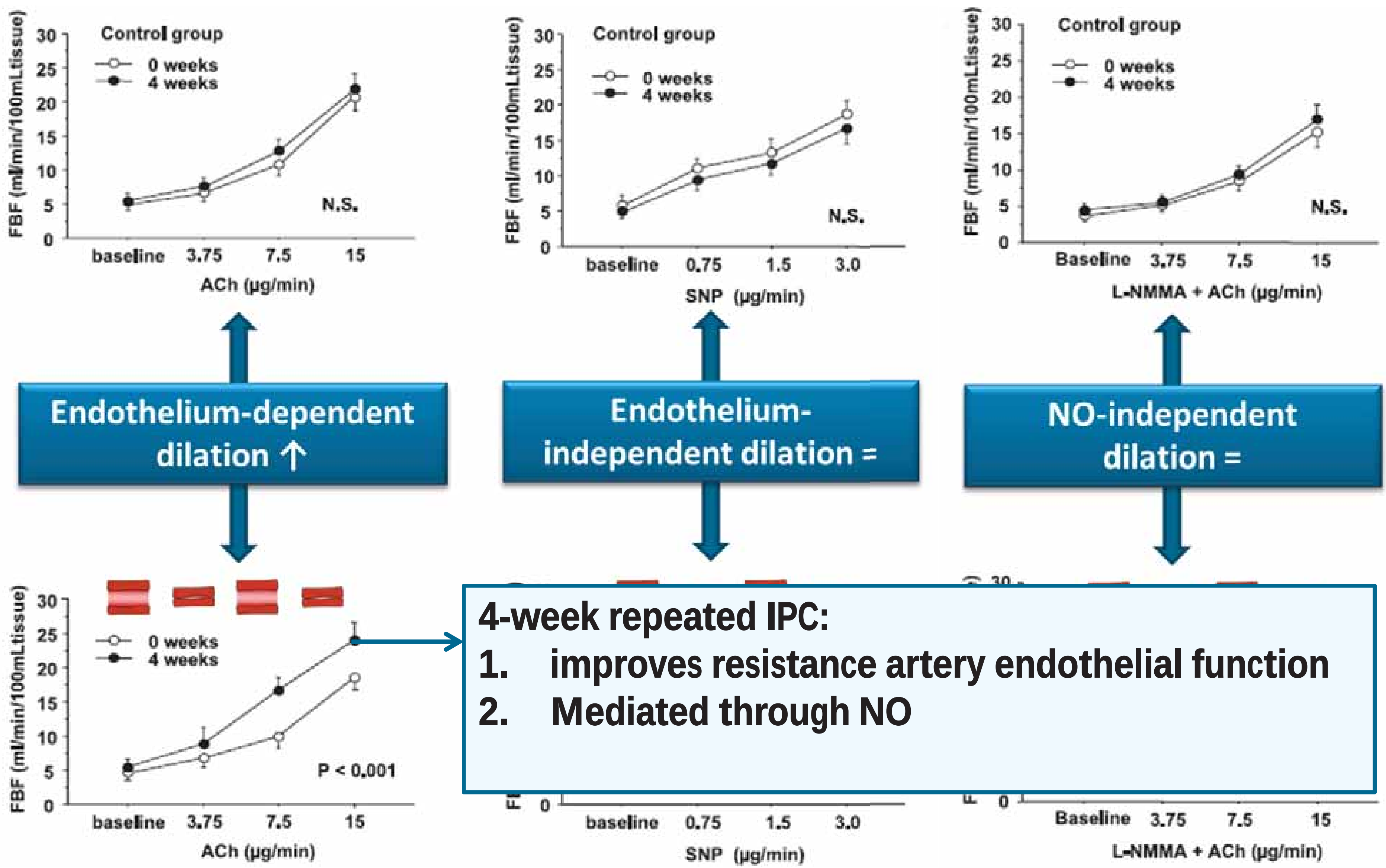
Repeated IPC: *resistance artery endothelial function ↑*



Design: 4-week daily, unilateral IPC
Subjects: 20 healthy young men
Measurements: intra-arterial infusion drugs (ACh, SNP, Ach+L-NMMA)

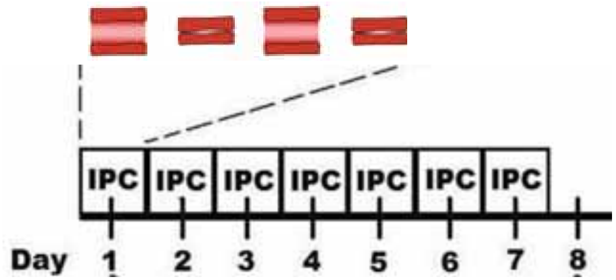
1. Kimura *Athero Tromb Vasc Biol* 2007

Repeated IPC: *resistance artery endothelial function ↑*

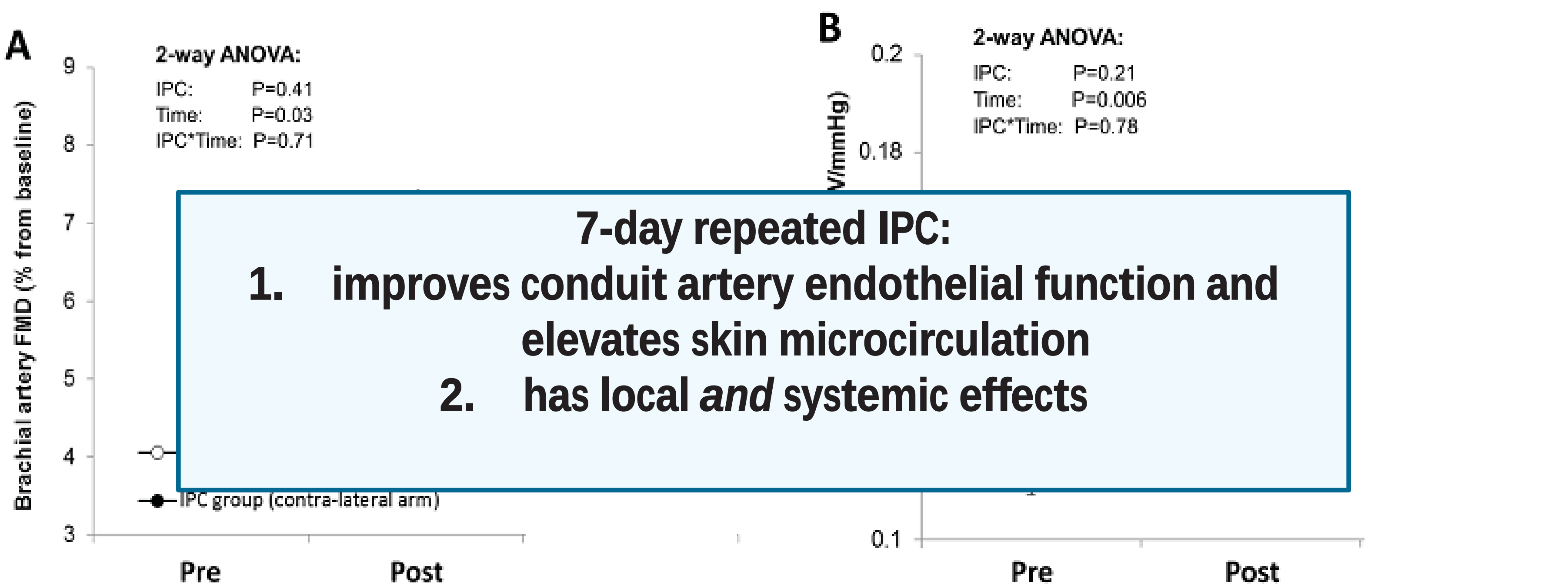


1. Kimura *Atherioscl Tromb Vasc Biol* 2007

Repeated IPC: *skin perfusion + endothelial function* ↑



Design: 1-week daily, unilateral IPC
Subjects: 13 healthy young men
Measurements: bilateral FMD + skin

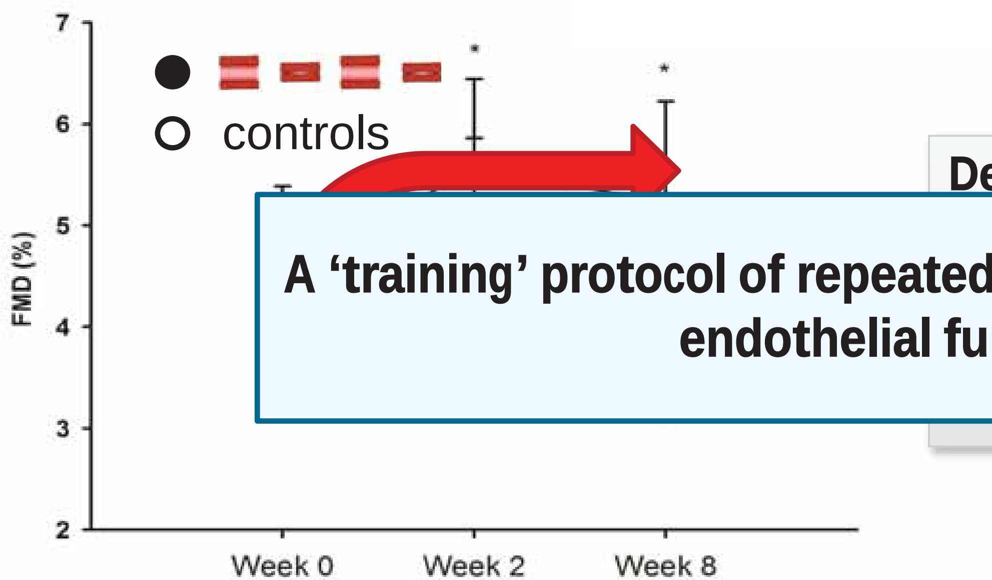


7-day repeated IPC:

1. **improves conduit artery endothelial function and elevates skin microcirculation**
2. **has local *and* systemic effects**

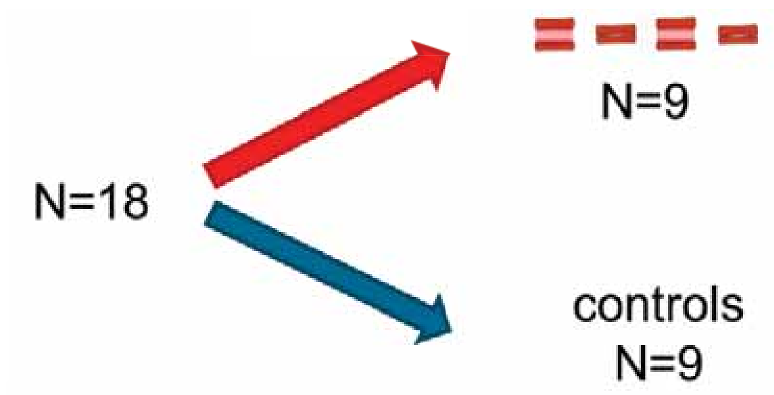
1. Jones *Am J Hypert* 2014

Repeated IPC: *improved function after ‘training’ protocol*



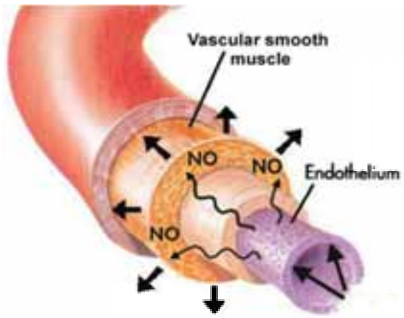
Design: Randomised controlled trial
C (3 p/wk)
n

A ‘training’ protocol of repeated IPC (8-weeks) improves endothelial function

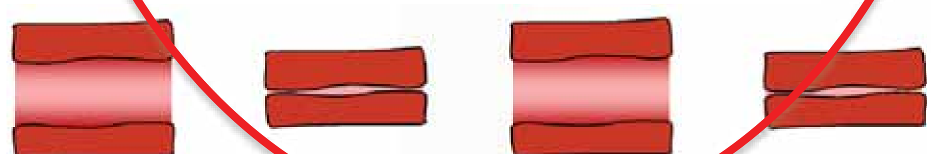


1. Jones *In Revision* 2014

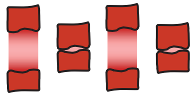
Plan



Ischemic preconditioning (3/4 x 5 min)



Ischemic preconditioning improves maximal performance

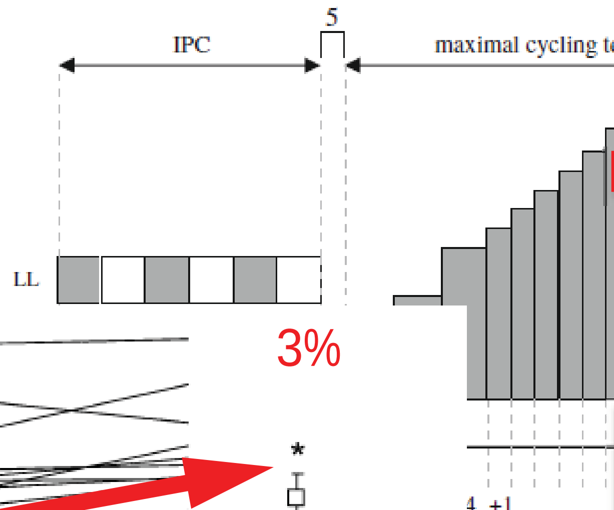


(Leg:3 x 5 min)

Bilateral

LOCAL EFFECT (IPC)

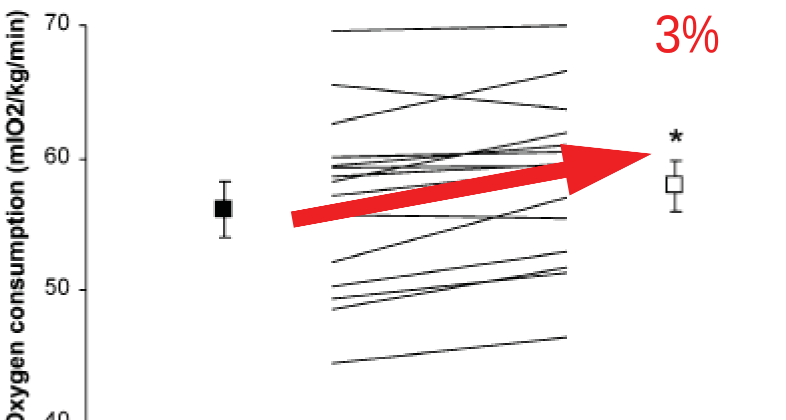
Enhanced maximal exercise performance



	Control	IPC	*P* value
VO_2max (ml/min per kg)	56.8 (6.8)	58.4 (6.2)	0.003
Maximal power output (W)	366 (62)	372 (59)	0.05
Ventilation (l/min)	143.4 (29.7)	148.9 (22.6)	*NS*
Respiratory Quotient	1.20 (0.1)	1.20 (0.1)	NS
HRmax (bpm)	183 (9)	183 (7)	NS
BPrest syst/diast (mmHg)	130/83	129/83	NS
BPmax syst/diast (mmHg)	177/66	173/68	NS
Lactate (mmol/l)	12.3 (3.6)	13.3 (3.5)	NS
VO_2 at 50 W (ml/min per kg)	15.4 (1.6)	15.6 (1.4)	NS
VO_2 at 100 W (ml/min per kg)	21.8 (2.0)	21.9 (2.2)	NS
VO_2 at 150 W (ml/min per kg)	29.1 (3.0)	29.2 (3.2)	NS

Values are expressed as mean (SD)

1.6%



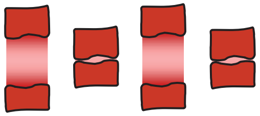
No effect on submaximal exercise levels

Patricia C. E. de Groot · Dick H. J. Thijssen · Manuel Sanchez · Reinier Ellenkamp · Maria T. E. Hopman

Eur J Appl Physiol (2010) 108:141–146
DOI 10.1007/s00421-009-1195-2

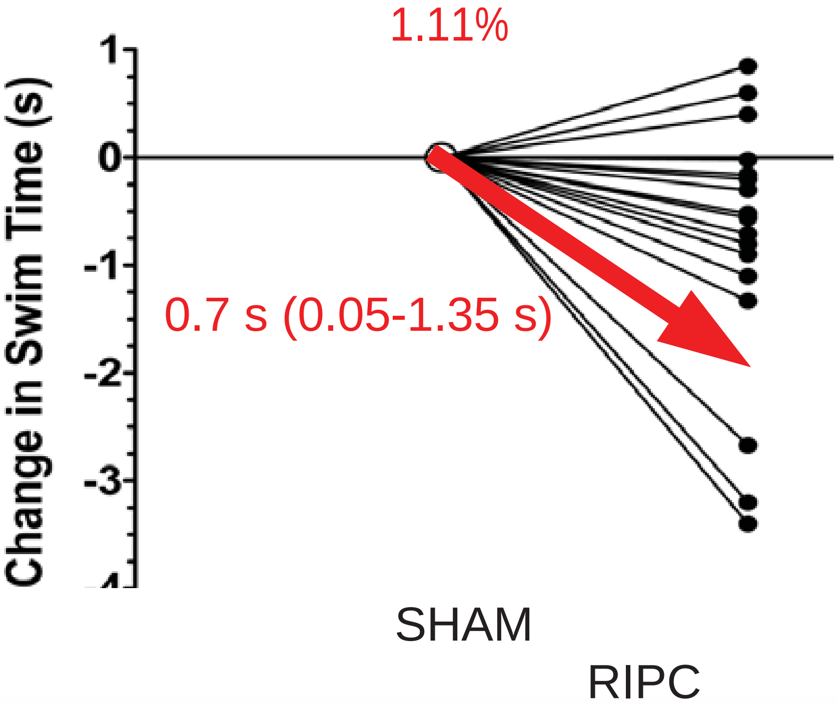
Remote preconditioning improves maximal performance in highly training athletes

Athletes



REMOTE EFFECT (RIPC)?

LOCAL EFFECT (IPC)?

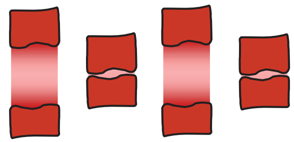


Enhanced maximal exercise performance

EMILIE JEAN-ST-MICHEL[1], CEDRIC MANLHIOT[1], JING LI[1], MICHAEL TROPAK[1], MARIE M. MICHELSEN[2], MICHAEL R. SCHMIDT[2], BRIAN W. MCCRINDLE[1], GREG D. WELLS[1], and ANDREW N. REDINGTON[1]

MEDICINE & SCIENCE IN SPORTS & EXERCISE®
Vol. 43, No. 7, pp. 1280–1286, 2011

Ischemic preconditioning of one arm enhances static and dynamic apnea



(Arm: 4 x 5 min)

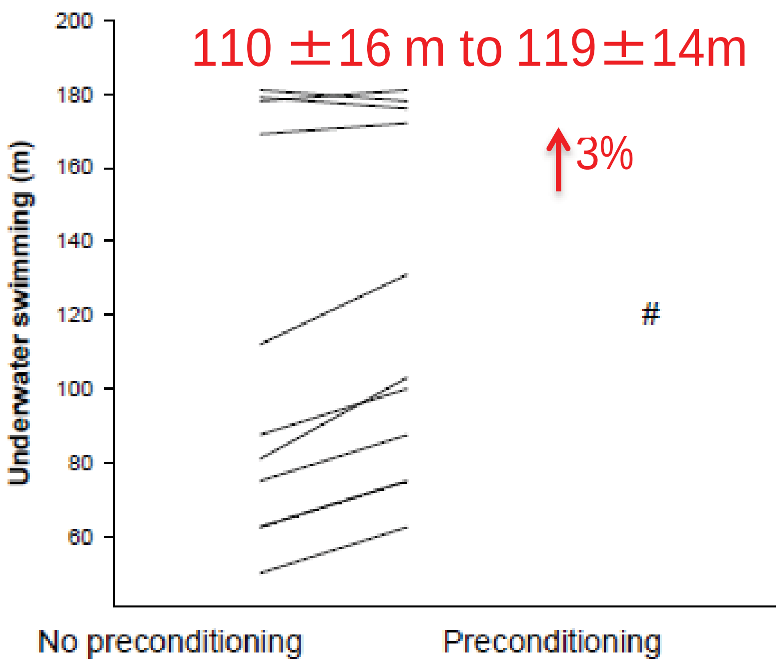
Unilateral

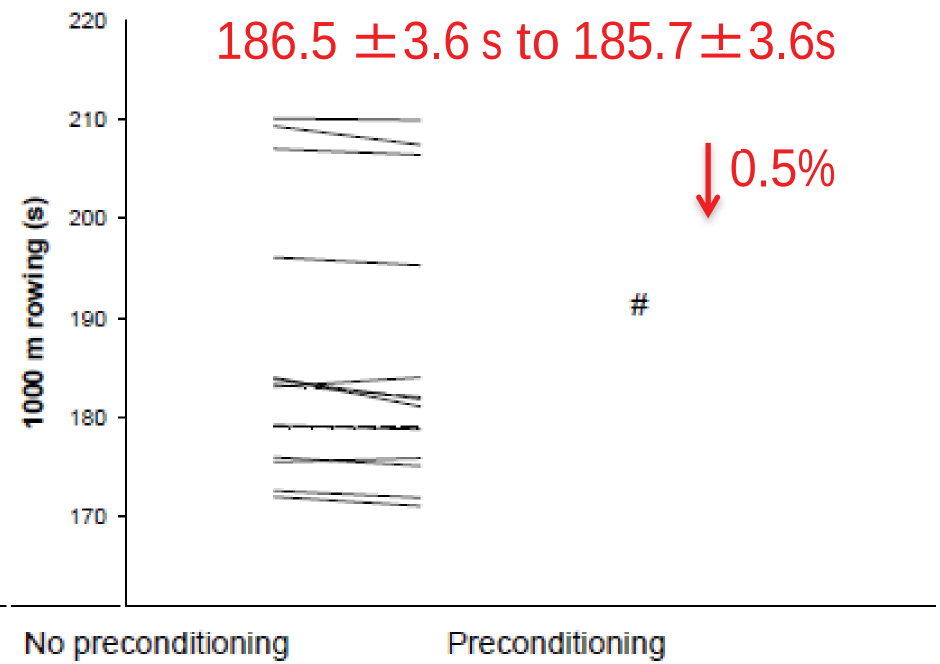
REMOTE EFFECT (RIPC)

LOCAL EFFECT (IPC)

Underwater swimming

Athletes



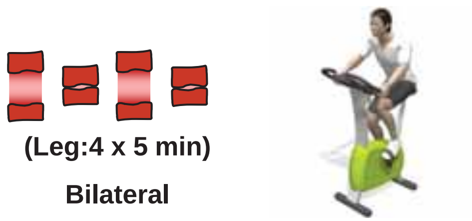


Kjeld et al., (2014) MSSE, 46:151-155

Ischemic preconditioning and warm-up???

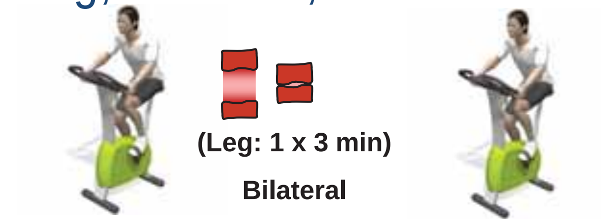
Control

IPC prior to max test

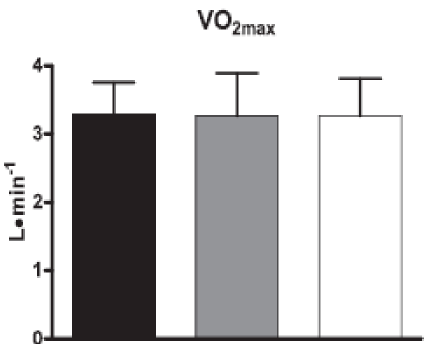


LOCAL EFFECT (IPC)

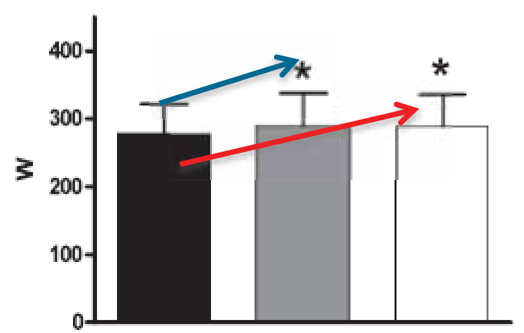
Cycling, then IPC, then max test



LOCAL EFFECT (IPC)

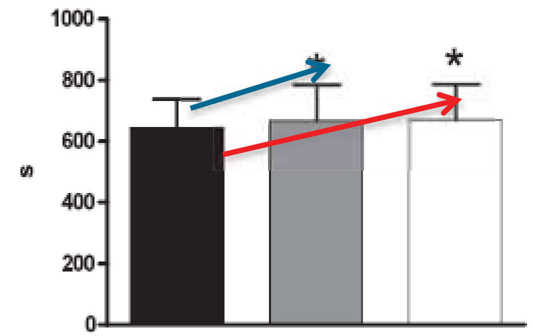


No change in maximal oxygen uptake



increase in workload with both exercise and IPC as warm up

increase in workload with IPC only as warm up



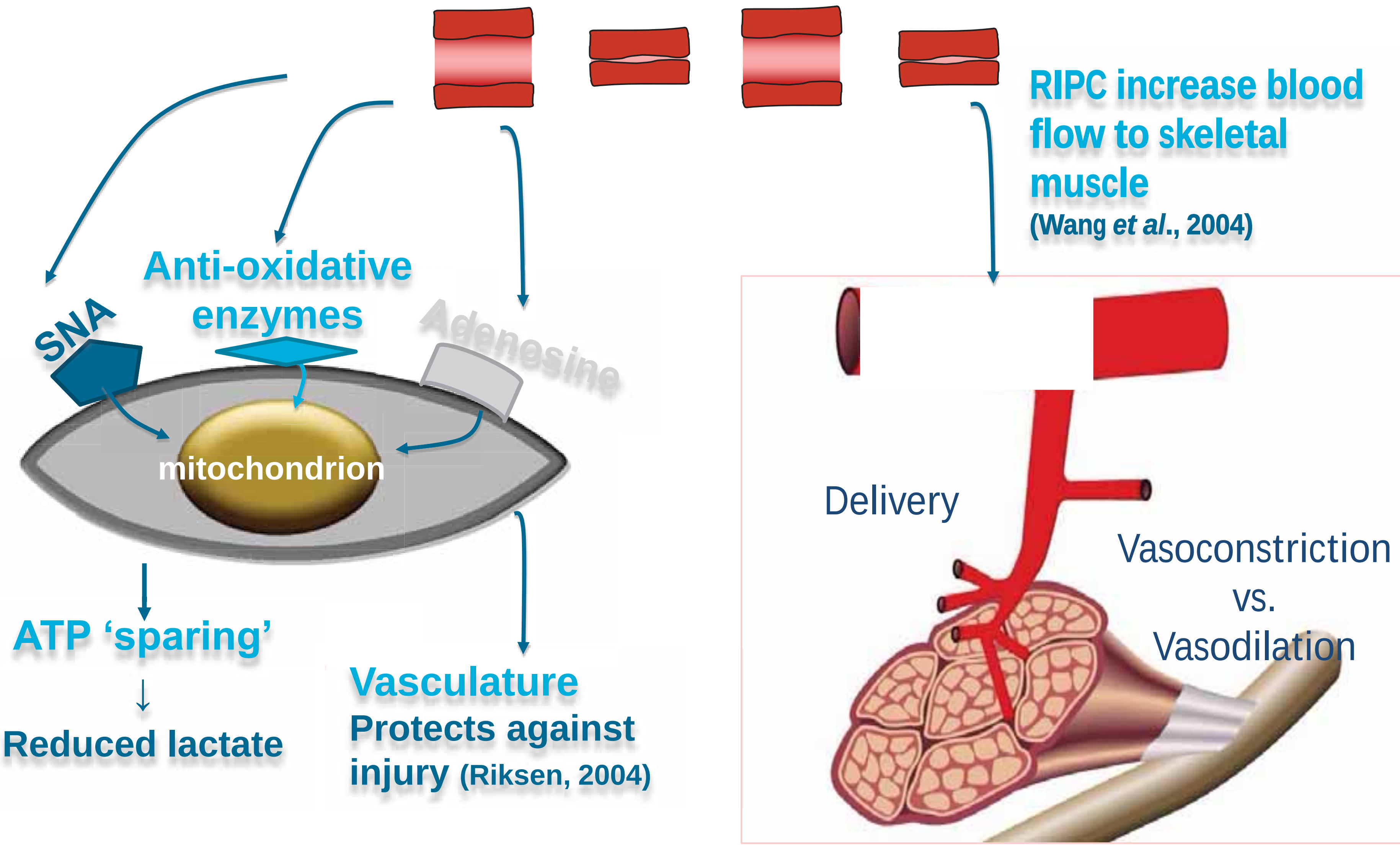
Exercised longer with both exercise and IPC as warm up

Exercised longer with IPC only as warm up

Antonio Crisafulli,[1,2] Flavio Tangianu,[2] Filippo Tocco,[1] Alberto Concu,[1] Ombretta Mameli,[2] Gabriele Mulliri,[2] and Marcello A. Caria[2]

J Appl Physiol 111: 530–536, 2011.
First published May 26, 2011; doi:10.1152/japplphysiol.00266.2011.

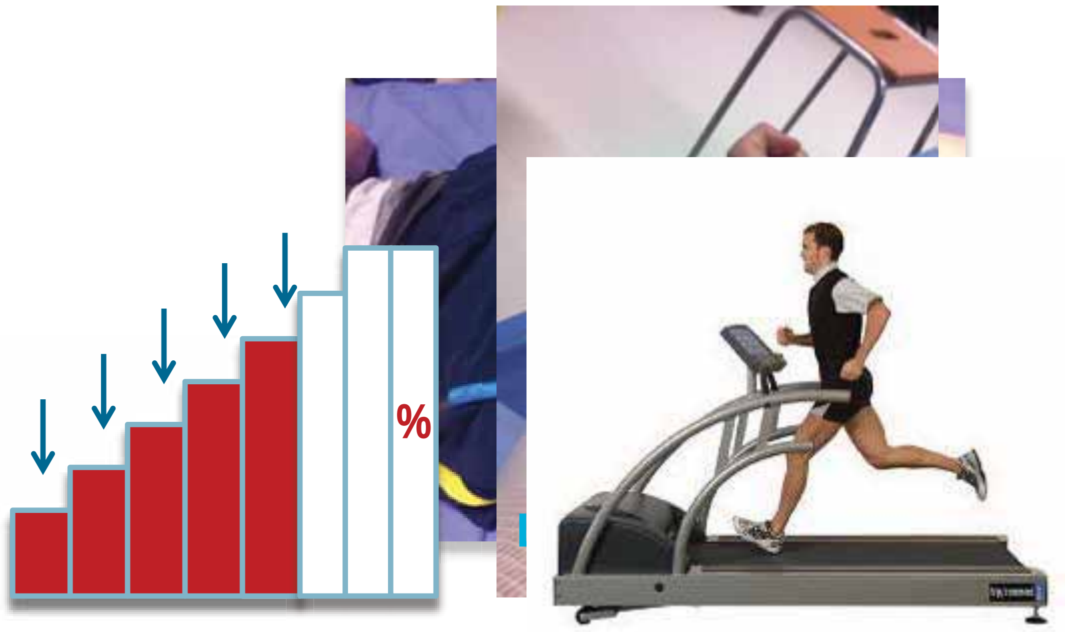
Potential mechanisms

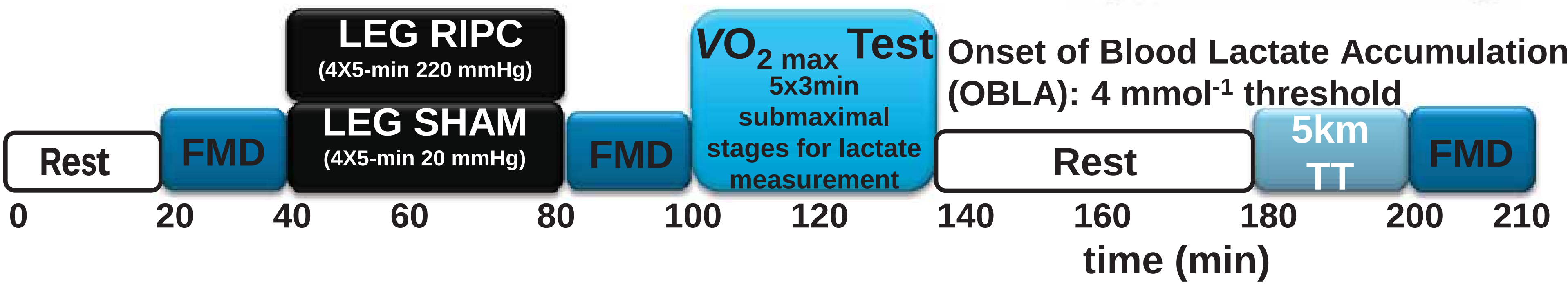


Are IPC performance improvements related to lactate accumulation or vascular function?

Moderately trained males

- **RIPC *vs.* SHAM**
- ***V*O2max Test (running)**
- ***Lactate***
- **5km Time-Trial (5km TT)**
- **Unilateral brachial FMD**

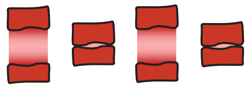




FMD = flow mediated dilation of brachial artery

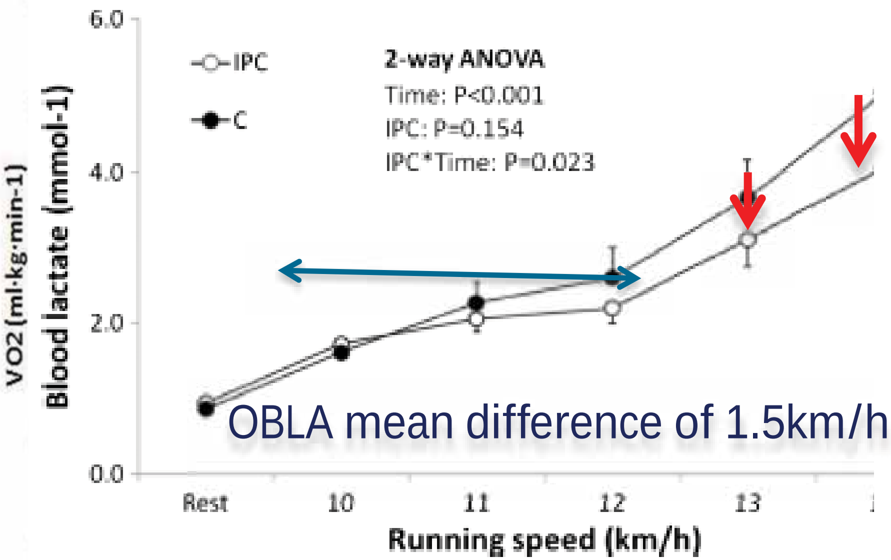
5km TT = 5000m treadmill time-trial

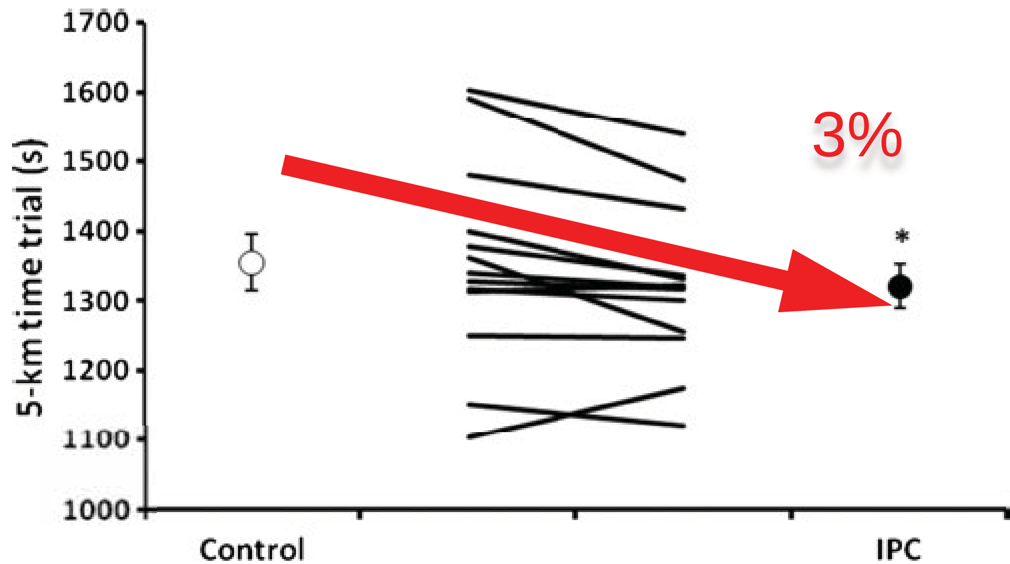
IPC attenuates lactate accumulation and improves running performance



(Leg: 4 x 5 min)

Bilateral
LOCAL EFFECT (IPC)





Max Test

IPC + Max Test

Time to Exhaustion unchanged

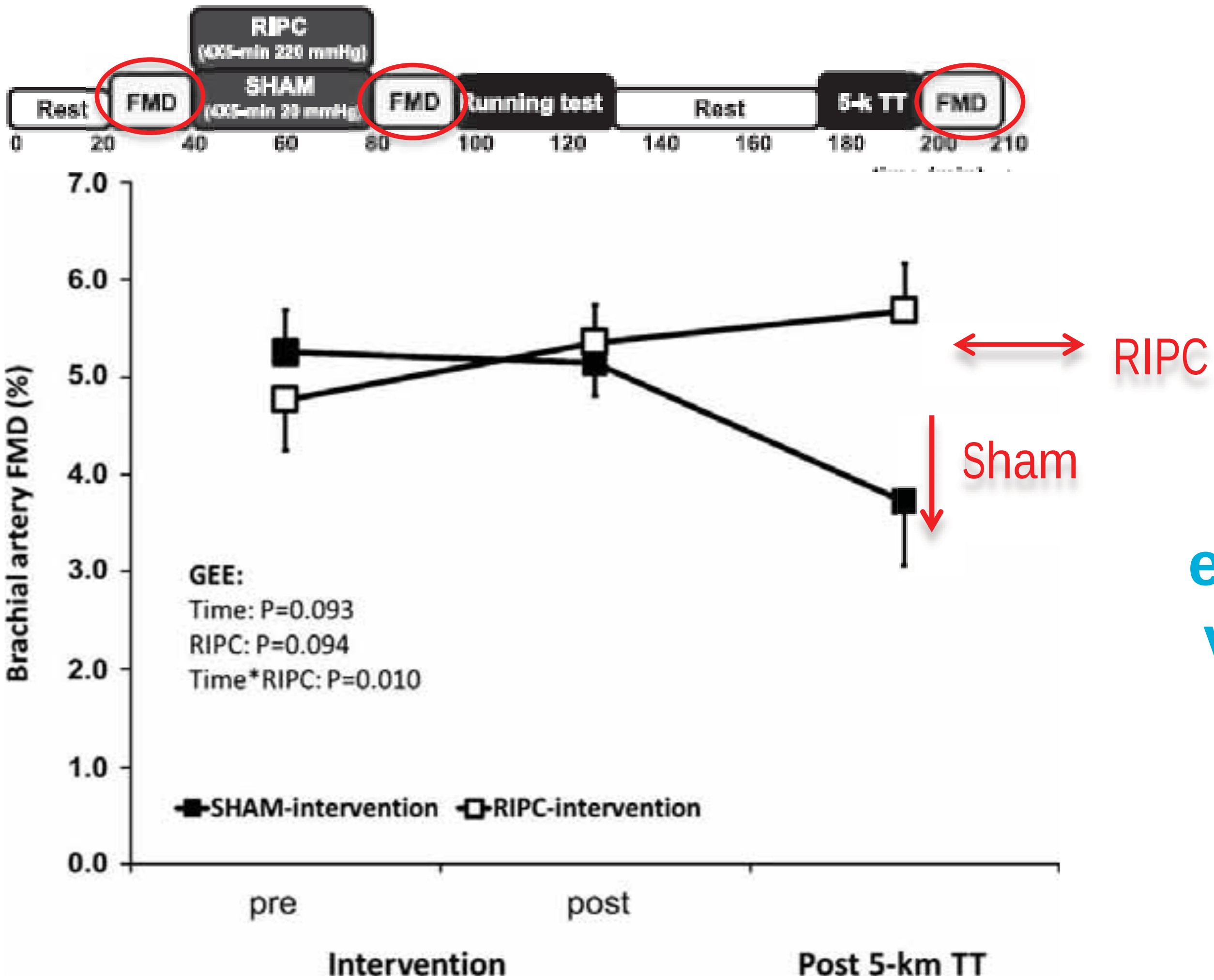
Reduced lactate accumulation?

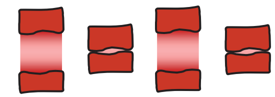
Improve 5km time-trial performance with local IPC?

TOM G. BAILEY[1], HELEN JONES[1], WARREN GREGSON[1], GREG ATKINSON[1,2], NIGEL TIMOTHY CABLE[1], and DICK H. J. THIJSSEN[1,3]

Med. Sci. Sports Exerc., Vol. 44, No. 11, pp. 2084–2089, 2012

RIPC prevents the reduction in brachial artery flow-mediated dilation after strenuous exercise





(Leg: 4 x 5 min)

Bilateral

REMOTE EFFECT (IPC)

RIPC prevents exercise-induced vascular injury?

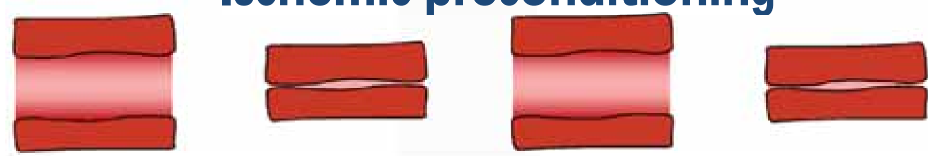
Tom G. Bailey,[1] Gurpreet K. Birk,[1] N. Timothy Cable,[1] Greg Atkinson,[1] Daniel J. Green,[1,2] Helen Jones,[1] and Dick H. J. Thijssen[1,3]

Am J Physiol Heart Circ Physiol 303: H533–H538, 2012.
First published June 22, 2012; doi:10.1152/ajpheart.00272.2012.

Interim summary

Improves performance? ✓

Ischemic preconditioning



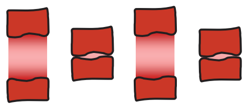
✓ Reduced lactate accumulation?

✓ Prevents exercise-induced vascular injury?

✓ Alters blood flow distribution?

What the most appropriate methodology to employ?

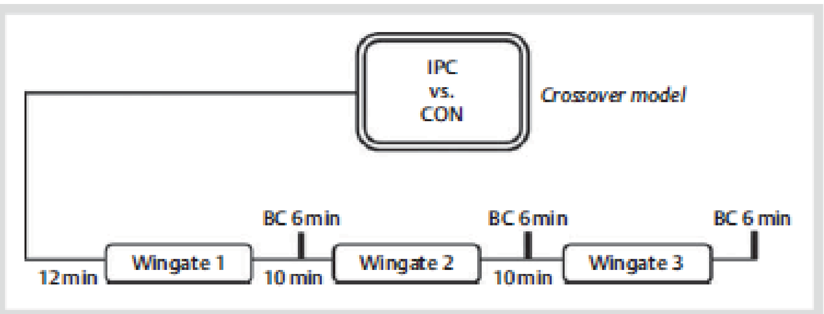
Is exercise duration and intensity important?



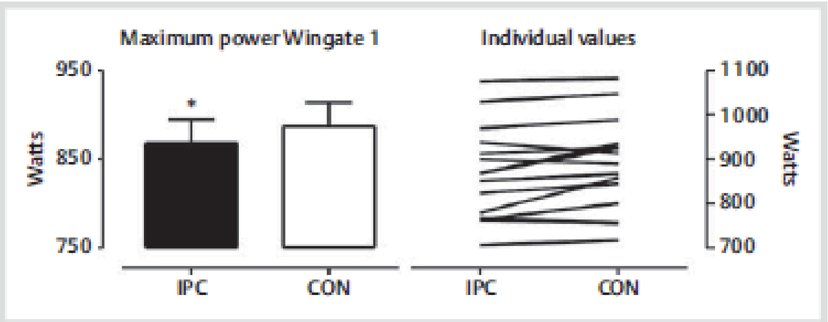
(Leg: 4 x 5 min)

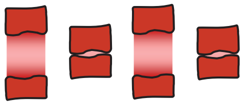
Bilateral

LOCAL EFFECT (IPC)



30 s against a 0.10kp/kg load

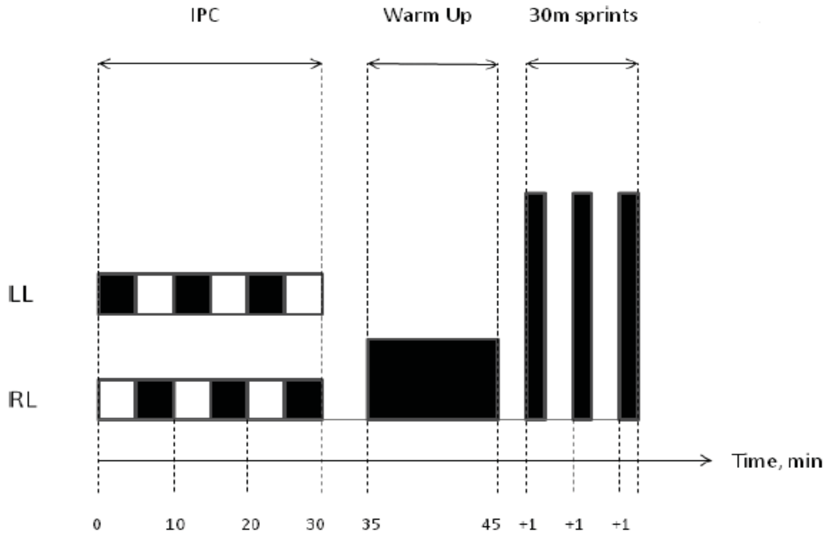




(Leg: 3 x 5 min)

Bilateral

LOCAL EFFECT (IPC)



	Control			Placebo			IPC		
	10-m	20-m	30-m	10-m	20-m	30-m	10-m	20-m	30-m
Mean	1.82	3.19	4.51	1.83	3.23	4.56	1.80	3.20	4.51
SD	0.15	0.15	0.25	0.14	0.17	0.28	0.16	0.21	0.29

Note: No significant differences were observed between treatment groups.

Very short duration, predominately anaerobic

R. C. Paixão[1,2], G. Ribeiro da Mota[1], M. Marocolo[1]

Published online: 2014
Int J Sports Med

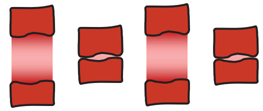
Neil Gibson, James White, Mhari Neish, and Andrew Murray

International Journal of Sports Physiology and Performance, 2013, 8, 671-676

Does REMOTE IPC improve performance?

Bailey *et al*., 2012

LOCAL EFFECT (IPC)

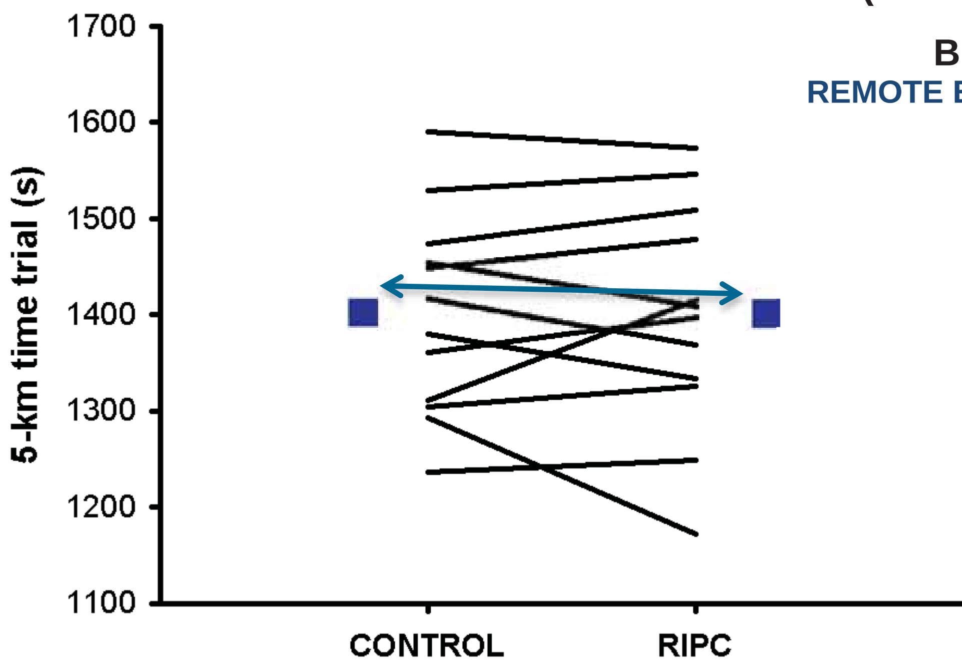


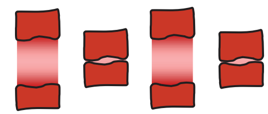
(LEG: 4 x 5 min)

Bilateral

5km time-trial 

Rest | **ARM RIPC** (4X5-min 220 mmHg) | **5km TT**

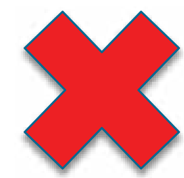




(ARM: 4 x 5 min)

Bilateral

REMOTE EFFECT (RIPC)



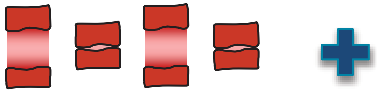
No improvement on 5km time-trial performance with RIPC?

Seeger et al., (2014) under review

IPC improves arm-crank exercise performance in spinal cord-injured individuals

CONTROL

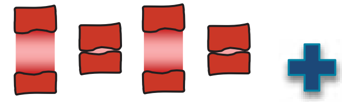
LOCAL EFFECT (IPC)



(Arm: 4 x 5 min)

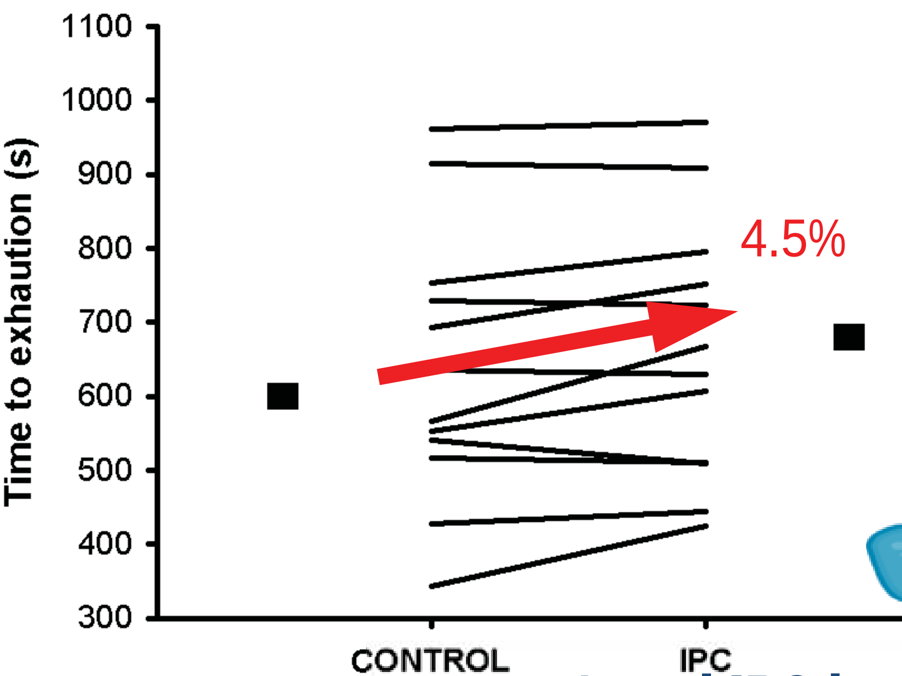
Bilateral

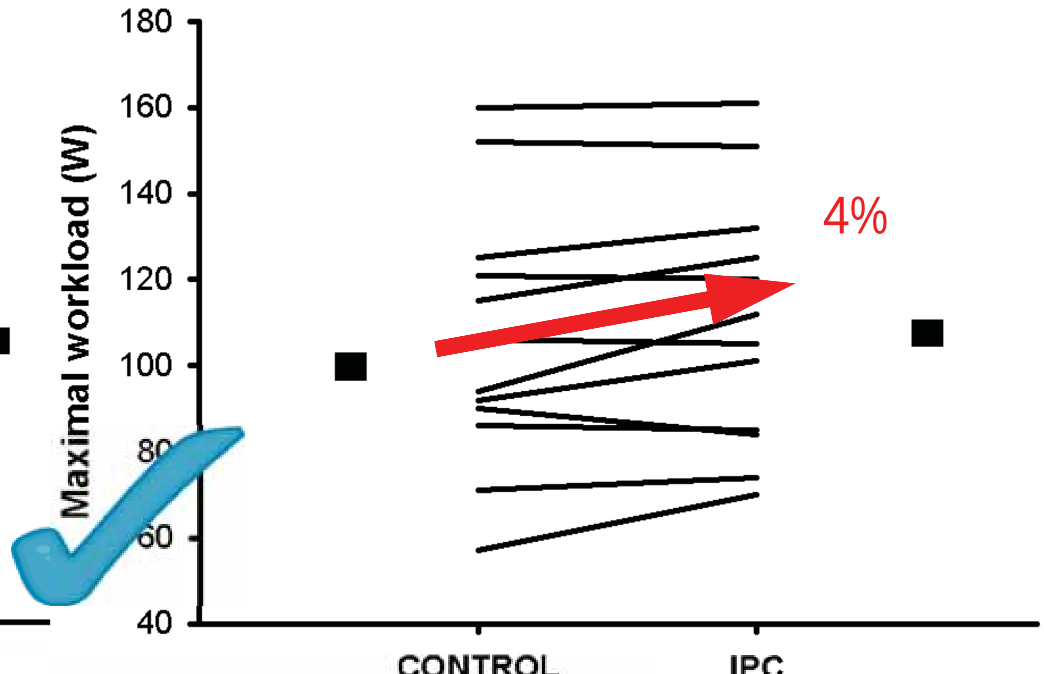
REMOTE EFFECT (RIPC)



(Leg: 4 x 5 min)

Bilateral





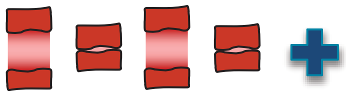
Local IPC improves performance

Seeger et al., (2014) under review

Ischemic preconditioning improves arm-crank exercise performance in spinal cord-injured individuals

CONTROL

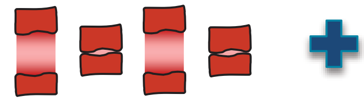
LOCAL EFFECT (IPC)



(Arm: 4 x 5 min)

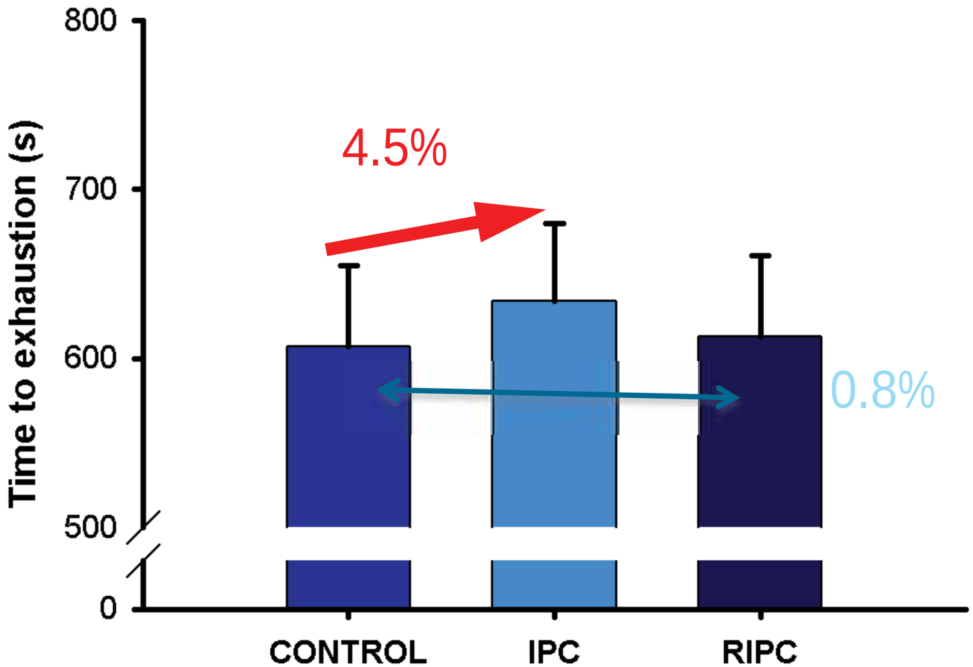
Bilateral

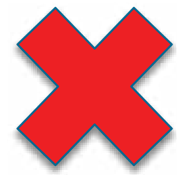
REMOTE EFFECT (RIPC)



(Leg: 4 x 5 min)

Bilateral





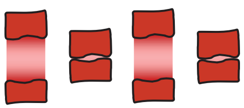
No improvement in performance with RIPC?

Seeger et al., (2014) under review

What is the optimal timing of IPC prior to performance?

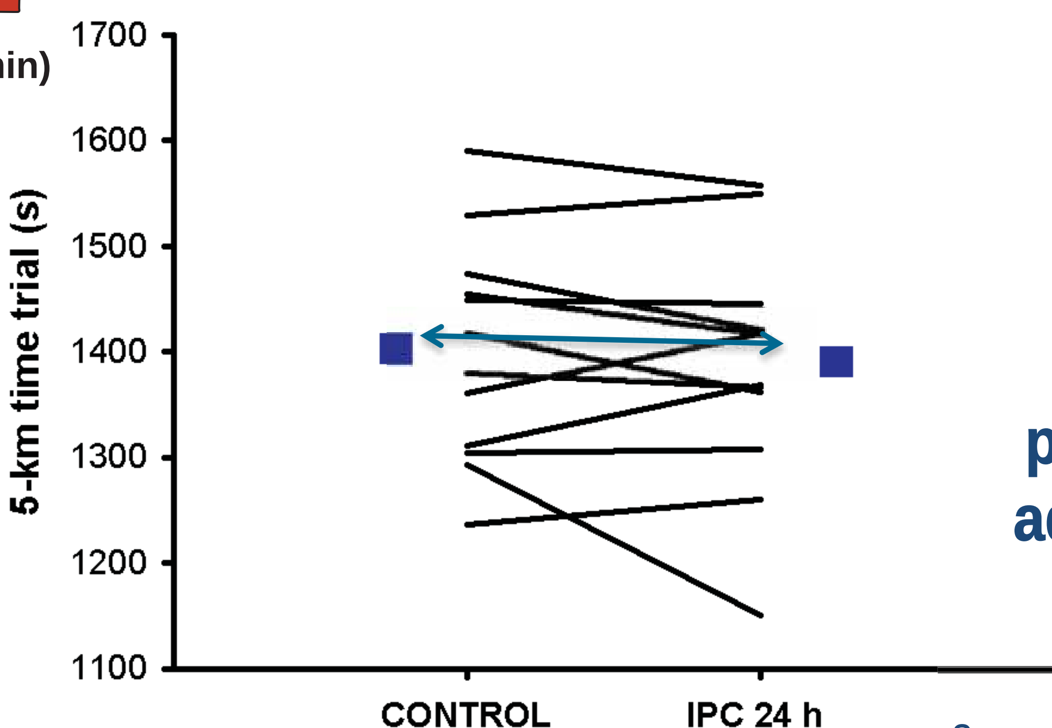
Rest | LEG IPC (4X5-min 220 mmHg) | 24 hours | 5km TT

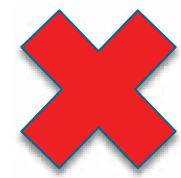
LOCAL EFFECT (IPC)



(Leg: 4 x 5 min)

Bilateral





No improvement in performance when IPC administered 24-h prior to exercise

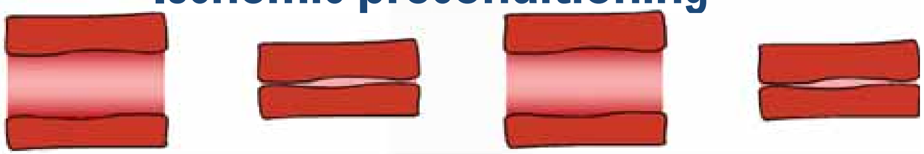
Seeger et al., (2014) under review

Different populations

Improves performance?

Timing

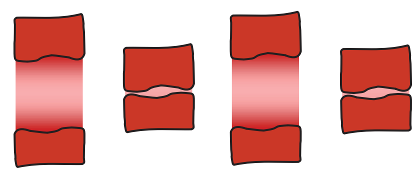
Ischemic preconditioning



Local vs remote

vs

Dose? More?



(4 x 5 min)

Unilateral or Bilateral

More studies needed!!!

Thank you for listening

Liverpool John Moores University:

Dr Helen Jones
Prof. Dick Thijssen
Dr. Nicola Hopkins
Joost Seeger
Prof. Danny Green
Dr Ellen Dawson

Radboud University:

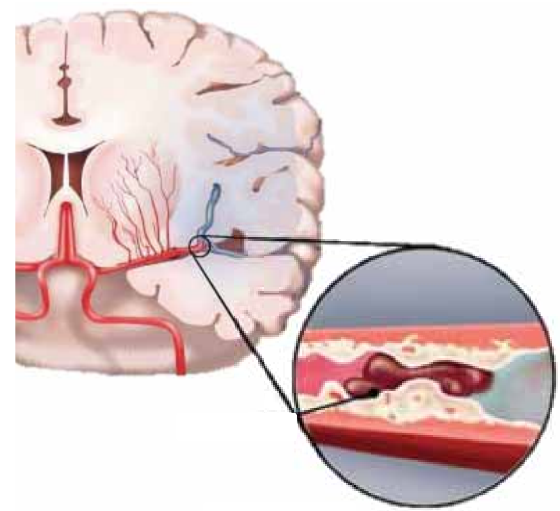
Prof. Dick Thijssen
Joost Seeger
Tim Schreuder
Dr. Michiel Warle
Dr. Thijs Eijsvogels
Dr. Niels Riksen
Prof. Maria Hopman

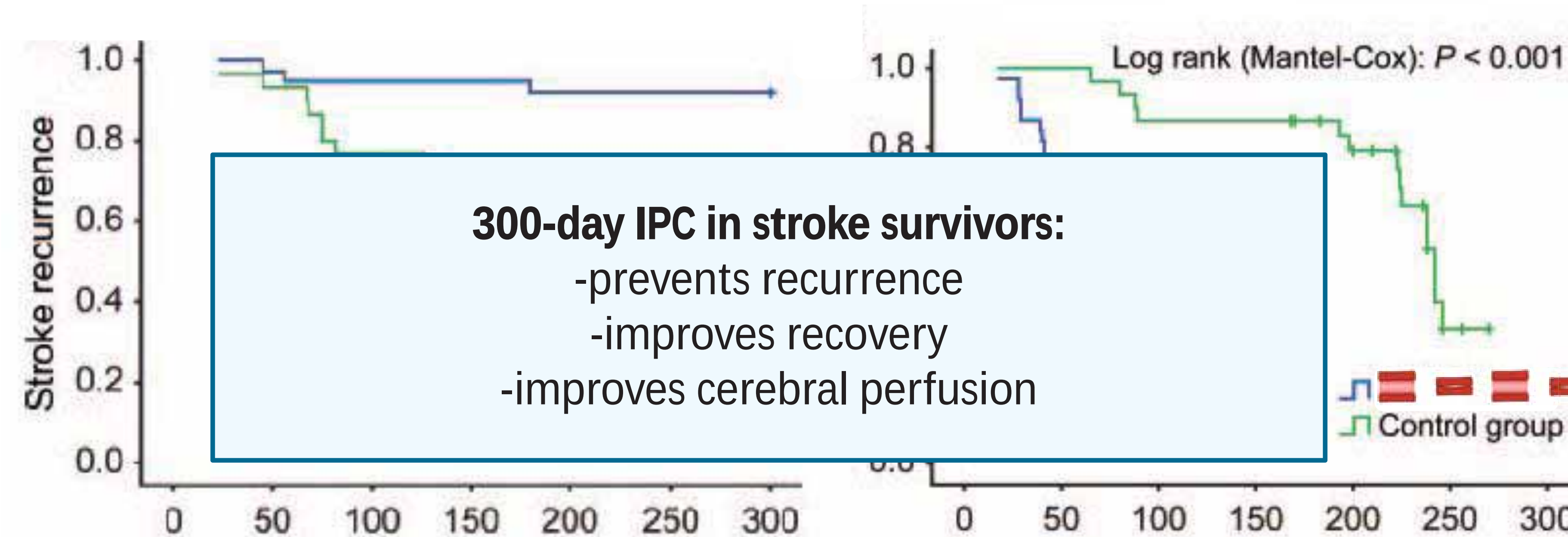
University of Western Australia:

Prof. Danny Green
Christopher Reed

Repeated IPC: *So what……*

Design: Randomised controlled trial
twice daily, 300-days IPC
(bilateral)
Subjects: 68 stroke survivors
(38 IPC, 30 controls)
Measurements: stroke recurrence,
cerebral perfusion

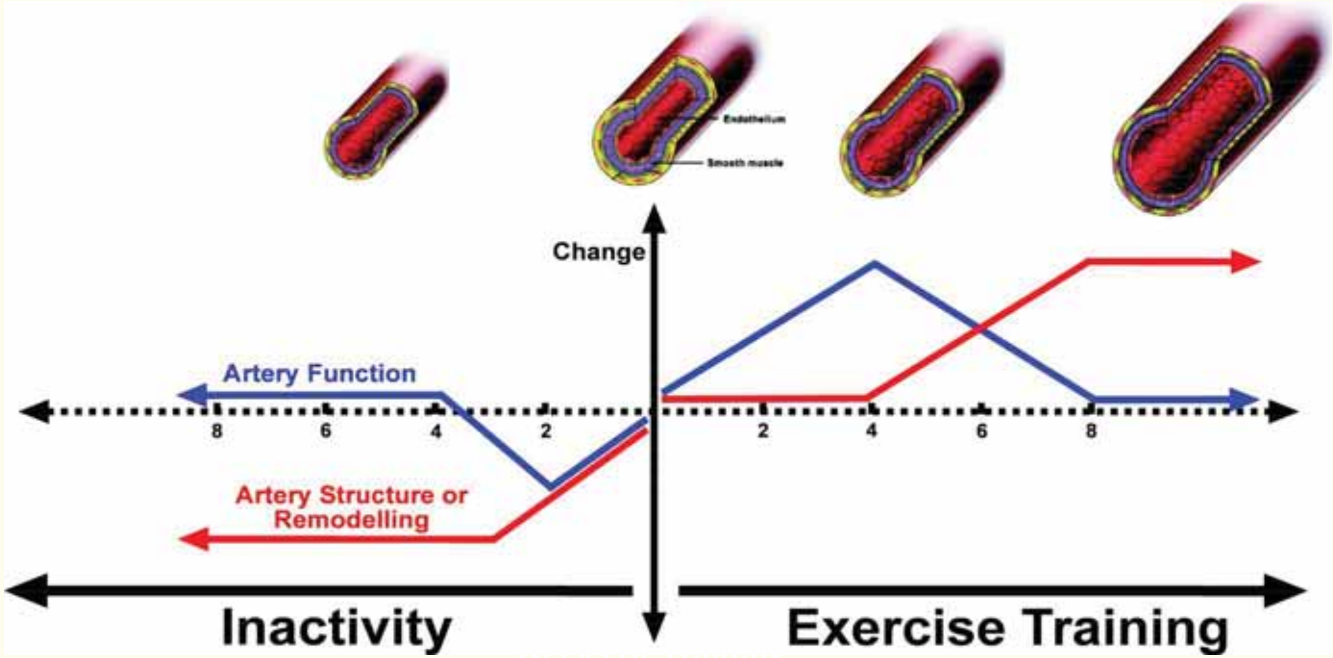




300-day IPC in stroke survivors:
-prevents recurrence
-improves recovery
-improves cerebral perfusion

1. Meng *Neurology* 2012

Functional Changes (↑in NO) Precede Structural Adaptations (↑in size)

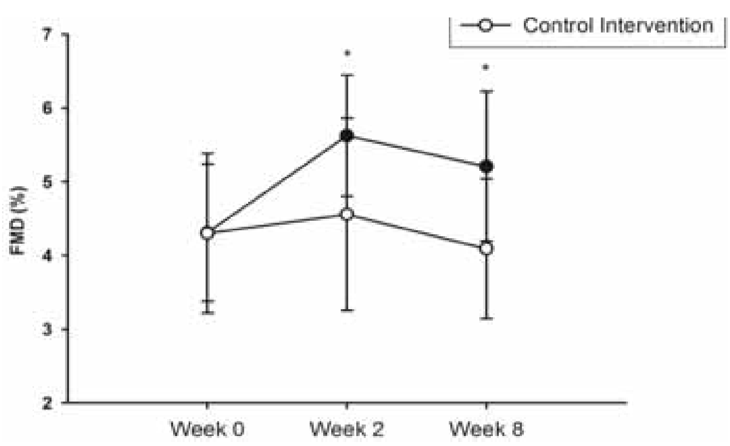


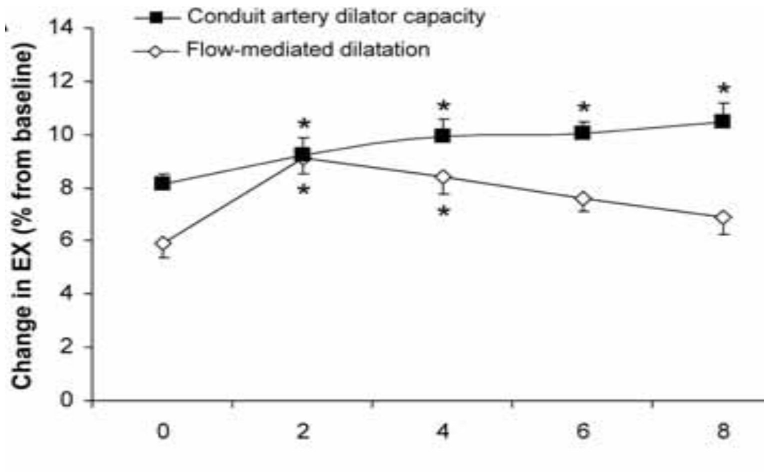
- Functional changes = repetitive ↑ in shear stress →↑ NO availability
- Structural changes = ↑ in arterial size → normalise shear rate

Both adaptation increase blood flow

Repeated IPC: *conclusion*

- Repeated IPC improves endothelial function:
  - Locally *and* systemically
  - Conduit *and* resistance arteries
  - Intensive (daily) *and* more practical protocols (3 p/week)





Stimulus IPC shares similarities with exercise

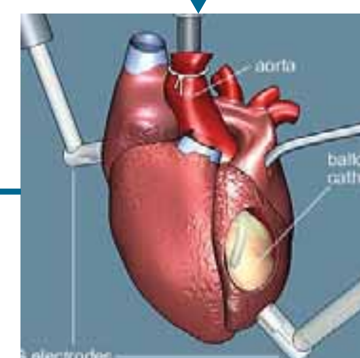
....

Is there a link?

IPC: *does exercise have IPC-like effects?*

Design: Cross-over design (1. IPC,
2. interval exercise)
Subjects: 12 healthy subjects
Measurements: infarct size (animals)

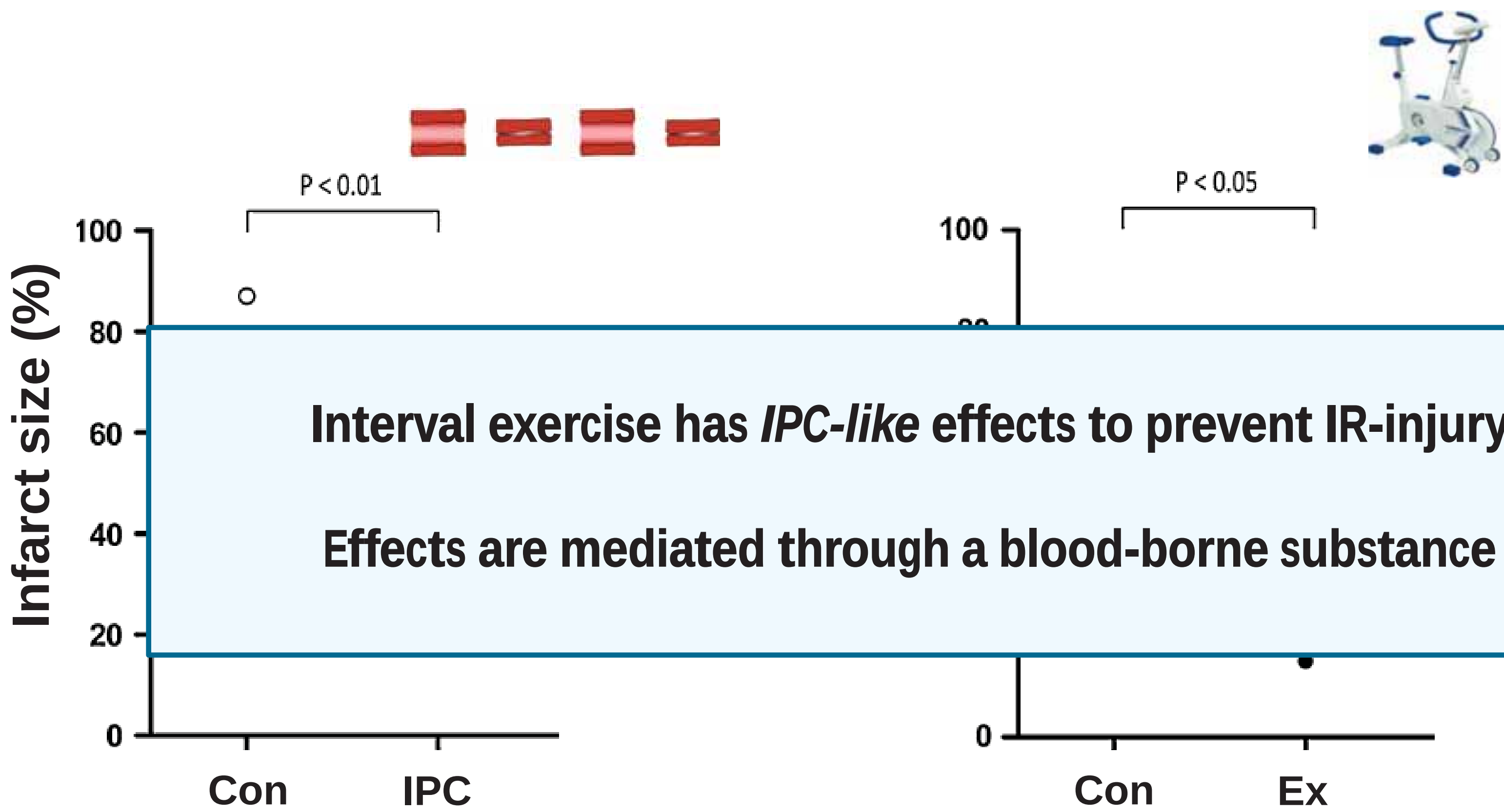
N=12



25-min perfusion
(Control, IPC, Exercise)
40-min ischemia
120-min reperfusion

1. Michelsen *Bas Res Cardiol* 2013

IPC: *relation to cardioprotection of exercise training*



Interval exercise has *IPC-like* effects to prevent IR-injury

Effects are mediated through a blood-borne substance

1. Michelsen *Bas Res Cardiol* 2013