Remote Ischemic Preconditioning (RIPC)

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Supervised by Dr Shum HP
15/9/2015

Ischemia

- A vascular disease due to restriction in blood supply
- Shortage of oxygen and vital nutrients
- Hampering normal cellular metabolism

- Reperfusion injury results in release of oxygen free radicals, cytokines and increase expression of adhesion molecules

What is preconditioning?

- Induce a stimulus near to but below the threshold of damage to the organism
- Tissues and organs develop resistance or tolerance to the same or similar noxious stimuli
- Preventing or reducing the damage it may induce

- Include many stimuli:
  - ischemia, hypoxia, hypothermia, drugs…..

ANNALS OF
INTERNAL MEDICINE

VOLUME 53 AUGUST, 1960 NUMBER 2

SOME CLINICAL ASPECTS OF LIFE AT HIGH ALTITUDES *

By ALBERTO HURTADO, M.D., *Lima, Peru*

CONTINUOUS exposure to a high-altitude environment, where the lowered partial pressure of the oxygen in the inspired air originates a certain degree of hypoxia, demands some adaptative mechanisms. These, in general, and in their main objectives, introduce an economy in the drop of the pO_2 gradient from alveolar air to tissue level, and make possible the acquisition and utilization of the oxygen in the cell metabolism. In our experience, and from observations carried out mainly in Morococha, Peru, at an altitude of 4,540 meters (14,900 feet), with an average barometric pressure of 444 mm. Hg, these mechanisms attain their highest degree of efficiency in the Indian natives, born and living permanently at a high level.[1] There is some evidence [2] that chemical processes in the tissues have a fundamental importance in what may be called "natural acclimatization."

But a high-altitude environment is not only a fertile field to study tolerance to hypoxia. When this is permanent, it may also give rise to functional and organic alterations, and may influence the development and characteristics of certain conditions which may be considered to be of a pathologic or clinical nature. We will comment very briefly on some of these latter aspects.

It has been demonstrated [3] that healthy people living permanently at high altitudes have a moderate but constant degree of pulmonary hypertension, in contrast to the presence of low systolic and diastolic pressures in the peripheral circulation (figure 1). The factors responsible for this elevation

* Received for publication April 15, 1960.
Presented as the Lilly Lecture at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 6, 1960.
From the Department of Pathological Physiology, and the Institute of Andean Biology, University of San Marcos Faculty of Medicine, Lima, Peru.
Requests for reprints should be addressed to Alberto Hurtado, M.D., Dean and Professor of Pathological Physiology, University of San Marcos Faculty of Medicine, Lima, Peru.

As early as in 1960

Reported lower incidence of myocardial infarction in people living at high altitude

2 subsequent animal studies

Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium

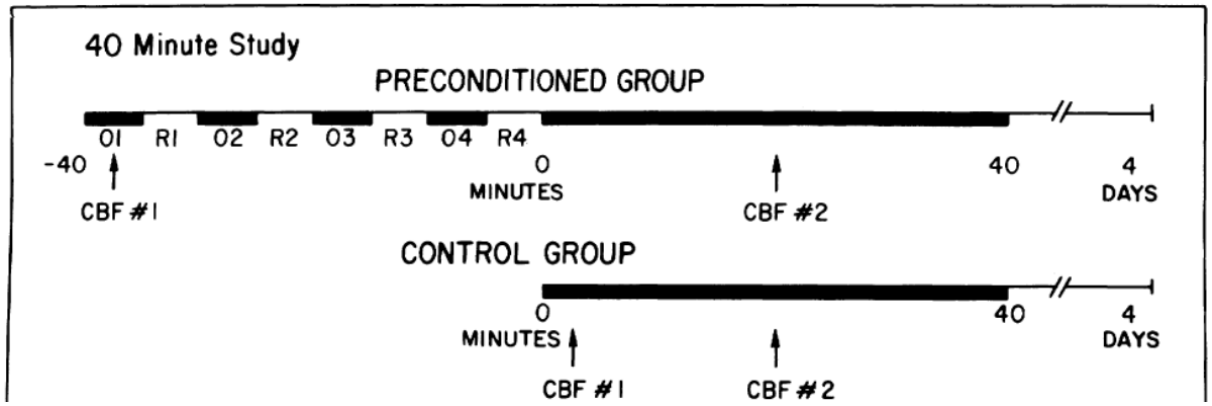
CHARLES E. MURRY, B.S., ROBERT B. JENNINGS, M.D., AND KEITH A. REIMER, M.D., PH.D.

Circulation 74. No. 5. 1124–1136. 1986.

ABSTRACT We have previously shown that a brief episode of ischemia slows the rate of ATP depletion during subsequent ischemic episodes. Additionally, intermittent reperfusion may be beneficial to the myocardium by washing out catabolites that have accumulated during ischemia.[1] Thus, we

2 subsequent animal studies

- 44 dogs
- Anaesthetized and intubated
- Thoracotomy and suspend the heart
- Snare the LCx
- Measure blood flow by radiolabeled microspheres
- Cardioversion if VF



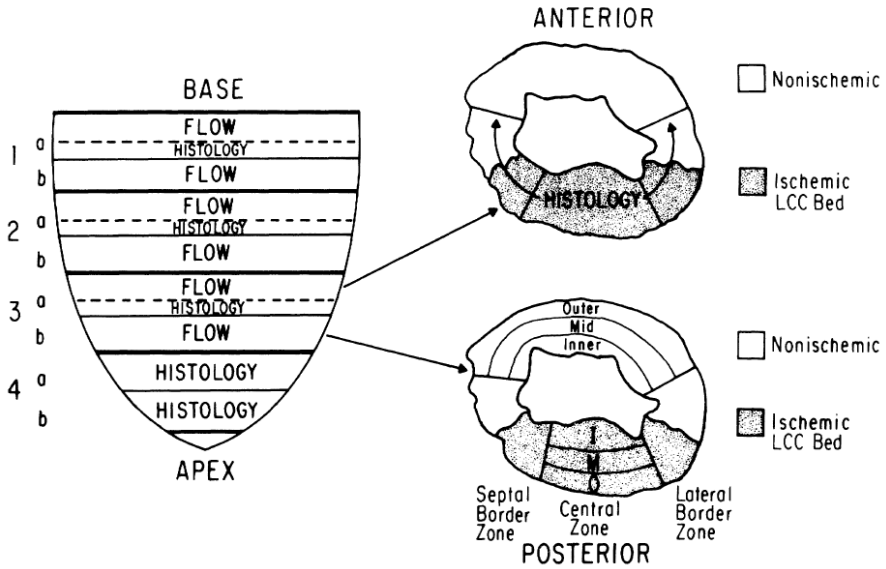
4 cycles 5-min ischemia

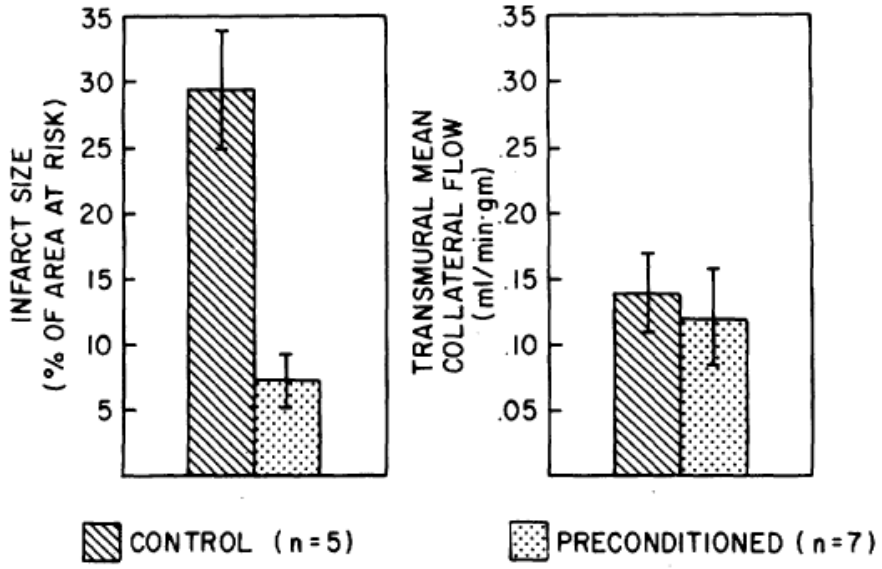
- Dogs were allowed to survive for 4 days to delineate the necrotic muscle
- Hearts were excised for postmortem

Circulation 74. No. 5. 1124–1136. 1986.

2 subsequent animal studies

- Results:





Some mechanism is protecting the heart from ischemia ?

Circulation 74, No. 5, 1124–1136, 1986.

2 subsequent studies

Hypoxic preconditioning of ischaemic canine myocardium

Yukitaka Shizukuda, Robert T Mallet, Shang-Chuin Lee, H Fred Downey

Cardiovascular Research 1 May 1992

- Demonstrated similar results in dogs
- Introduced the term "hypoxic preconditioning"

Evolution

- From intra-cardiac to inter-organ (Remote)
- From ischemic to non-ischemic trigger
- From pre- to per-/ post-conditioning

- Started to have human studies
- Initially mainly cardiac, some brain/ vascular
- Later on some focused on kidney

From intra-oragn to inter-organ

Myocardial protection by brief ischemia in noncardiac tissue

by Ben C.G. Gho, Regien G. Schoemaker, Mirella A. van den Doel, Dirk J. Duncker, and Pieter D. Verdouw

Circulation Volume 94(9):2193-2200
November 1, 1996

Bradykinin mediates cardiac preconditioning at a distance

Am J Physiol Heart Circ Physiol
278: H1571–H1576, 2000.

REGIEN G. SCHOEMAKER AND CAROLINE L. VAN HEIJNINGEN
Department of Pharmacology, Faculty of Medicine and Health Sciences, Erasmus University, NL-3000 DR Rotterdam, The Netherlands

Sites of action of adenosine in interorgan preconditioning of the heart

DAVID A. LIEM, PIETER D. VERDOUW, HARALD PLOEG, SHAHLA KAZIM, AND DIRK J. DUNCKER
Experimental Cardiology, Thoraxcenter, Erasmus University Rotterdam, 3000 DR Rotterdam, The Netherlands

Received 27 November 2001; accepted in final form 14 February 2002

Transient Limb Ischemia Induces Remote Ischemic Preconditioning In Vivo

R.K. Kharbanda, MRCP; U.M. Mortensen, MD; P.A. White, PhD; S.B. Kristiansen, MD; M.R. Schmidt, MD; J.A. Hoschtitzky, MSc, MRCSEd; M. Vogel, MD, PhD; K. Sorensen, MD; A.N. Redington, MD, FRCP; R. MacAllister, MD, FRCP

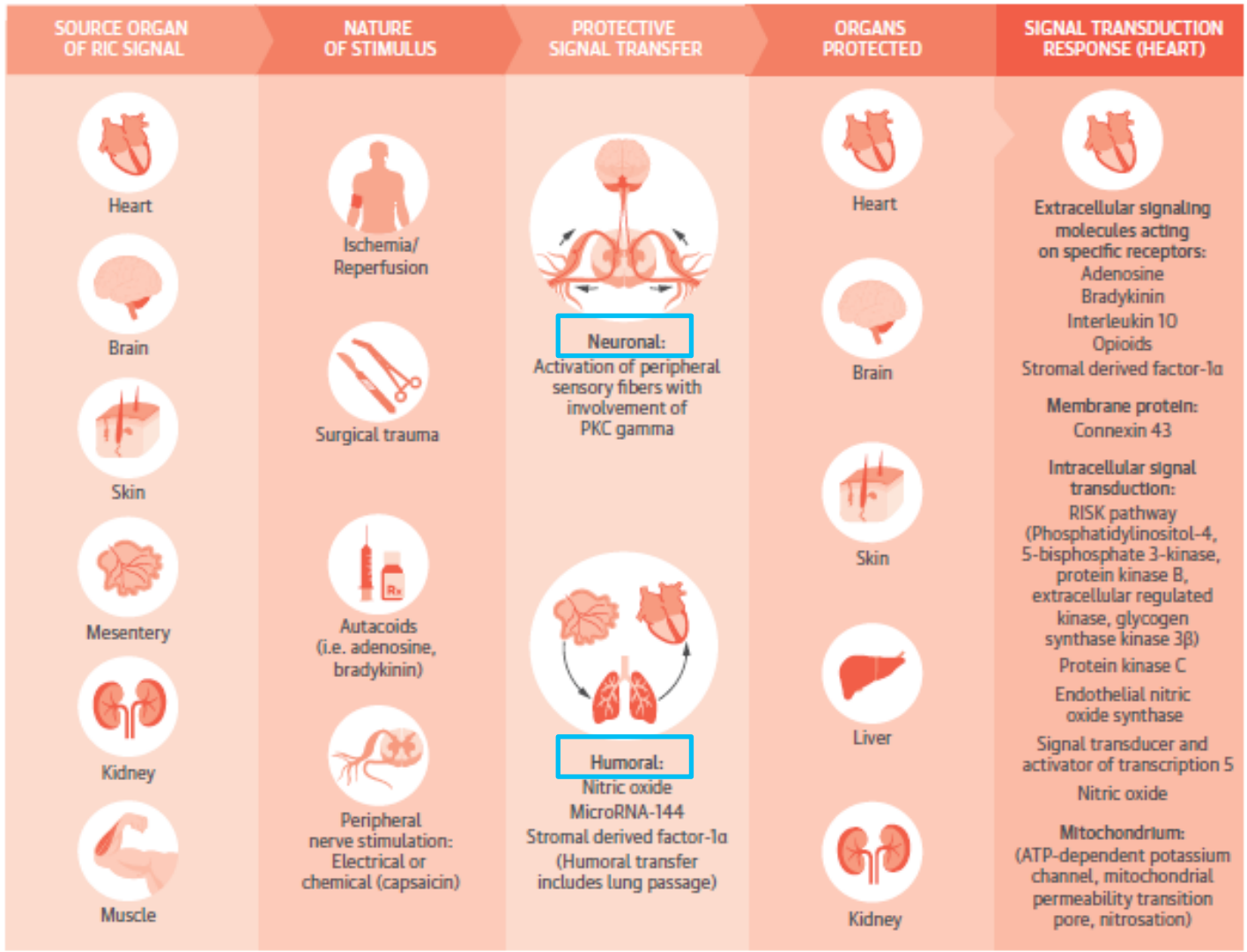
Circulation. 2002;106:2881-2883

What is REMOTE ischemic preconditioning?

- Brief episodes of ischemia-reperfusion in one vascular bed

- Protect a distant organ against a subsequent longer ischemic insult

CENTRAL ILLUSTRATION **Signal Transduction of Remote Ischemic Conditioning**



Heusch, G. et al. J Am Coll Cardiol. 2015; 65(2):177-95.

ATP = adenosine triphosphate; microRNA = microribonucleic acid; PKC = protein kinase C; RIC = remote ischemic conditioning; RISK = reperfusion injury salvage kinase.

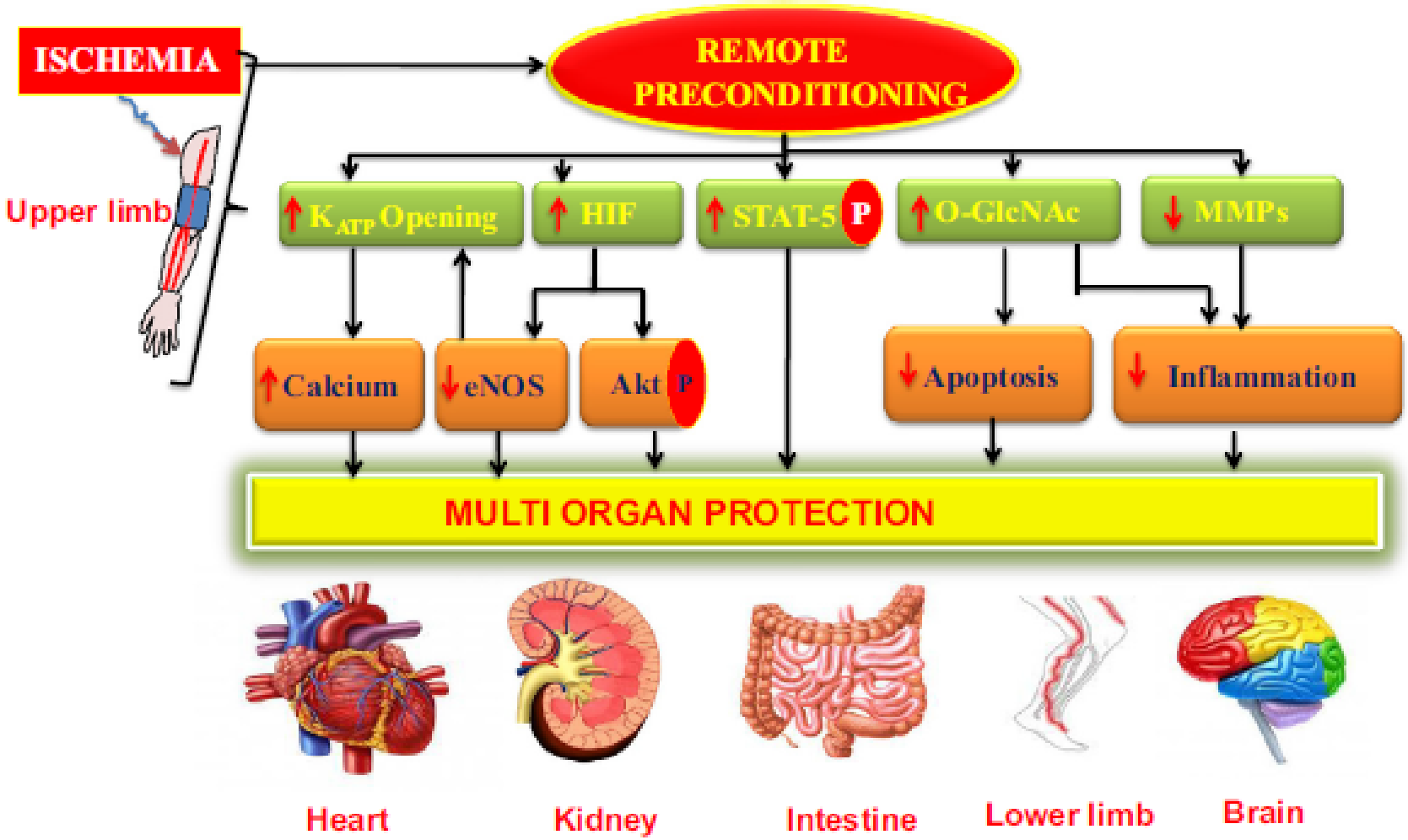


Fig. 1. Representation of RIPC-induced multi-organ protection and possible mechanisms.

Use of RIPC in cardiovascular surgery

Occupied most of the studies about RIPC

Remote preconditioning and major clinical complications following adult cardiovascular surgery: Systematic review and meta-analysis☆

International Journal of Cardiology 176 (2014) 20–31

- 23 trials of RIPC in 2200 patients
- undergoing major cardiovascular surgery

- RIPC did not have significant effect on clinical end points
- But sample size limited the results

Remote preconditioning and major clinical complications following adult cardiovascular surgery: Systematic review and meta-analysis ☆

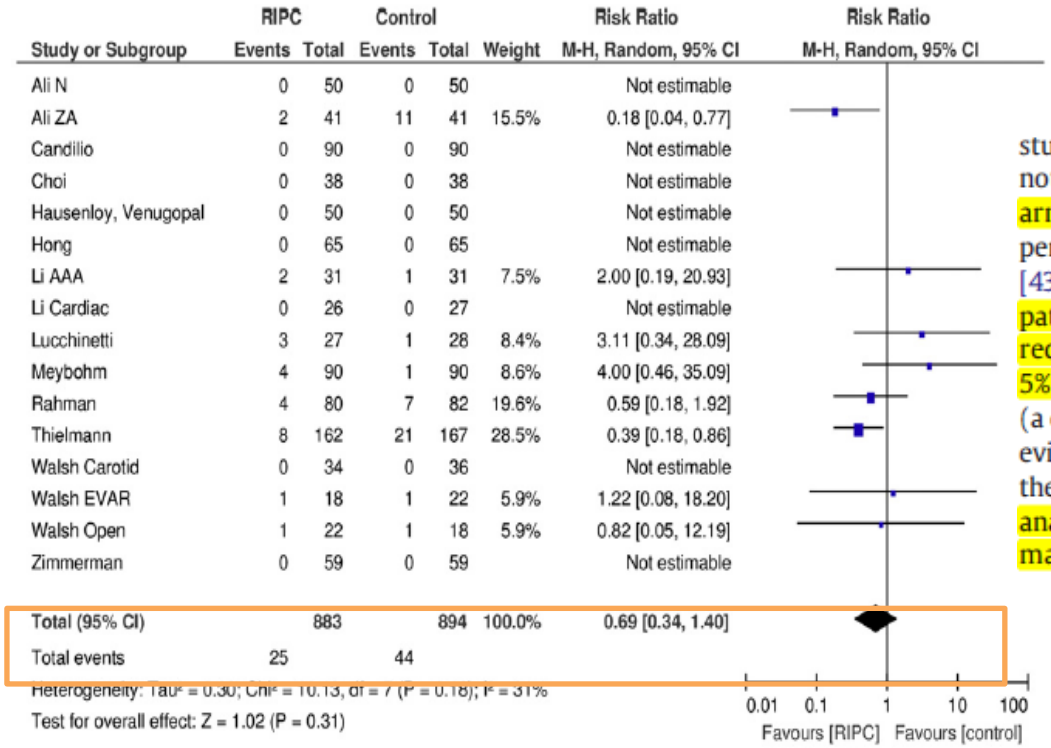
International Journal of Cardiology 176 (2014) 20–31

Table 1
Details of prior systematic reviews and meta-analyses on RIPC and cardiovascular surgery.

Author year	Procedure types	Number of included CVS trials	Number of included CVS patients	Outcomes reported	Results
Takagi [8] 2008	CVS	4	184	Biomarkers	Significant reduction in cardiac biomarkers
Takagi [9] 2011	CVS	9	482	Biomarkers, mortality and peri-operative MI	Significant reduction in cardiac biomarkers but no clinical benefit
Yetgin [10] 2012	PCI and CABG	13 — also included 4 PCI trials	891 — not including PCI	Biomarkers	Significant reduction in cardiac biomarkers
Alreja [11] 2012	CVS and PCI	13 — also included 4 PCI trials	814 — not including PCI	Biomarkers and MI, CVA, AF, ventricular arrhythmia, CHF, inotrope usage, HD need, mortality	Significant reduction in biomarkers and MI rate across CVS and PCI studies
Pilcher [12] 2012	Cardiac surgery	10	693	Biomarkers and mortality	Significant biomarker reduction only
Zhou [13] 2012	Cardiac surgery	15	1155	Biomarkers and mortality, MV duration, ICU LOS, hospital LOS	Significant biomarker reduction only
Brevoord [14] 2012	CVS and PCI	19 — also included 4 PCI trials	1166 — not including PCI	Biomarkers and mortality, CVA, MI, AF, kidney injury, hospital LOS, ICU LOS	Significant reduction in biomarkers and MI rate.
D'Ascenzo [15] 2012	CABG	9	704	Biomarkers and length of hospital stay	Significant cardiac biomarker reduction.
Yang [16] 2013	Cardiac surgery	19	1234	Biomarkers, mortality, complications, hospital and ICU LOS.	Significant cardiac biomarker reduction.
Heusch [5] 2013	Cardiac surgery and PCI	20	1239	Biomarkers	Most studies found benefits at biomarker level.
Yasin [17] 2014	Cardiac surgery	25	1762	Biomarkers, kidney injury, lung injury, mortality, ICU and hospital LOS, ventilation time.	Significant cardiac biomarker reduction.

Remote preconditioning and major clinical complications following adult cardiovascular surgery: Systematic review and meta-analysis☆

International Journal of Cardiology 176 (2014) 20–31



Study or Subgroup	RIPC Events	RIPC Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ali N	0	50	0	50		Not estimable
Ali ZA	2	41	11	41	15.5%	0.18 [0.04, 0.77]
Candilio	0	90	0	90		Not estimable
Choi	0	38	0	38		Not estimable
Hausenloy, Venugopal	0	50	0	50		Not estimable
Hong	0	65	0	65		Not estimable
Li AAA	2	31	1	31	7.5%	2.00 [0.19, 20.93]
Li Cardiac	0	26	0	27		Not estimable
Lucchinetti	3	27	1	28	8.4%	3.11 [0.34, 28.09]
Meybohm	4	90	1	90	8.6%	4.00 [0.46, 35.09]
Rahman	4	80	7	82	19.6%	0.59 [0.18, 1.92]
Thielmann	8	162	21	167	28.5%	0.39 [0.18, 0.86]
Walsh Carotid	0	34	0	36		Not estimable
Walsh EVAR	1	18	1	22	5.9%	1.22 [0.08, 18.20]
Walsh Open	1	22	1	18	5.9%	0.82 [0.05, 12.19]
Zimmerman	0	59	0	59		Not estimable
Total (95% CI)		883		894	100.0%	0.69 [0.34, 1.40]
Total events	25		44			

Heterogeneity: Tau² = 0.30; Chi² = 10.13, df = 7 (P = 0.18); I² = 31%

Test for overall effect: Z = 1.02 (P = 0.31)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours [RIPC] Favours [control]

study reflects sample size. However, there are grounds for optimism — notably, we found that the incidence of peri-operative MI in the RIPC arm was almost half that of the control arm (2.8% versus 4.9%). As peri-operative MI in cardiac surgery occurs with a frequency of 4–5% [43,44], a reduction by half would be clinically important. About 1200 patients would be required in each arm of a trial to confirm that RIPC reduces peri-operative MI rates from 4% to 2% with 80% power at the 5% significance level. While there was some heterogeneity in the cohort (a combination of cardiac and vascular surgery patients), there was no evidence of statistical heterogeneity in relation to the MI analysis and the funnel plot did not suggest bias. Therefore, the results of the MI analysis provide an encouraging indication that remote preconditioning may affect clinical end-points in cardiovascular surgery patients.

The use of RIPC to prevent AKI

RIPC and AKI

AJKD

Original Investigation

Remote Ischemic Preconditioning for Prevention of Acute Kidney Injury: A Meta-analysis of Randomized Controlled Trials

Yi Yang, PhD, MD,[1,] Xia-bing Lang, BS,[1,*] Ping Zhang, MD,[1] Rong Lv, MD,[1] Yong-fei Wang, BS,[2] and Jiang-hua Chen, MD[1]*

Am J Kidney Dis. 64(4):574-583.

Background: Remote ischemic preconditioning (RIPC) to prevent acute kidney injury (AKI) following cardiac and vascular interventions is a controversial practice.

Study Design: We conducted a systematic review and meta-analysis using the MEDLINE database (1966 through November 2013), EMBASE (1988 through November 2013), and Cochrane Library database.

Setting & Population: Patients undergoing cardiac and vascular interventions.

Selection Criteria for Studies: Randomized controlled trials comparing patient outcome with or without RIPC for prevention of AKI following cardiac and vascular interventions.

Intervention: RIPC using an inflatable tourniquet around the limb or cross-clamping the iliac arteries versus non-RIPC.

Outcomes: AKI, need for renal replacement therapy, postoperative kidney biomarkers, in-hospital mortality, and length of intensive care unit and hospital stay.

Am J Kidney Dis. 64(4):574-583. © *2014 by the National Kidney Foundation, Inc.*

2007 - 2013

Table 1. Demographic Data of Included Trials

Study	No. of Patients[a]	Mean Age (y)[a]	Surgical Procedure	Contrast Dose (mL)	RIPC Procedures	Baseline Scr[a,b] (μmol/L)	AKI Definition
Ali et al[17] (2007)	41/41	74/75	Elective open AAA repair	None	Cross-clamping of iliac arteries	102/101	Peak Scr > 177 μmol/L
Walsh et al[18] (2009)	18/22	74/76	Elective endovascular AAA repair	309/286	Inflatable tourniquet around lower limbs	95/94	Decrease in eGFR ≥ 20% from baseline
Hoole et al[19] (2009)	104/98	63.2/61.8	Elective PCI	196.7/187.5	Inflatable tourniquet around upper arms	NA	Scr > 25% increase from baseline
Rahman et al[20] (2010)	80/82	63/65	CABG	None	Inflatable tourniquet around upper arms	98.1/96.4	Scr > 0.5 mg/dL increase from baseline
Thielmann et al[21] (2010)	27/26	63.4/64.1	Elective CABG	None	Inflatable tourniquet around upper arms	NA	NA
Walsh et al[22] (2010)	22/18	75/72	Elective open AAA repair	None	Cross-clamping of iliac arteries	97/88	Decrease in eGFR ≥ 20% from baseline
Zimmerman et al[23] (2011)	59/59	62/65	Elective cardiac surgery with CPB	None	Inflatable tourniquet around lower limbs	82.2/84.0	AKIN criterion
Choi et al[24] (2011)	38/38	57/60	Elective complex valvular heart surgery	None	Inflatable tourniquet around lower limbs	80.4/81.3	AKIN criterion
Er et al[25] (2012)	50/50	73.2/72.7	Elective coronary angiography	124/103	Inflatable tourniquet around upper arms	144.1/143.2	Scr ≥ 25% or ≥0.5 mg/dL increase from baseline
Young et al[26] (2012)	48/48	65.5/64.4	High-risk cardiac surgery with CPB	None	Inflatable tourniquet around upper arms	102/95	RIFLE criterion
Pedersen et al[27] (2012)	54/51	1.0/0.9	Complex congenital heart disease surgery	None	Inflatable tourniquet around lower limbs	35/32	RIFLE criterion
Lucchinetti et al[28] (2012)	27/28	59/62	Elective CABG	None	Inflatable tourniquet around lower limbs	91.7/88.0	NA
Luo et al[29] (2013)	101/104	59.2/59.3	Elective PCI	154/145	Inflatable tourniquet around upper arms	NA	Scr ≥ 25% increase from baseline

Abbreviations: AAA, abdominal aortic aneurysm; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; NA, not available; PCI, percutaneous coronary intervention; RIFLE, risk, injury, failure, loss, and end-stage disease; RIPC, remote ischemic preconditioning; Scr, serum creatinine.

[a]RIPC group/control group.

[b]Baseline Scr refers to Scr level in all trials except Pedersen et al,[27] which refers to plasma creatinine level.

13 trials ; 1,334 participants

Am J Kidney Dis. 64(4):574-583.

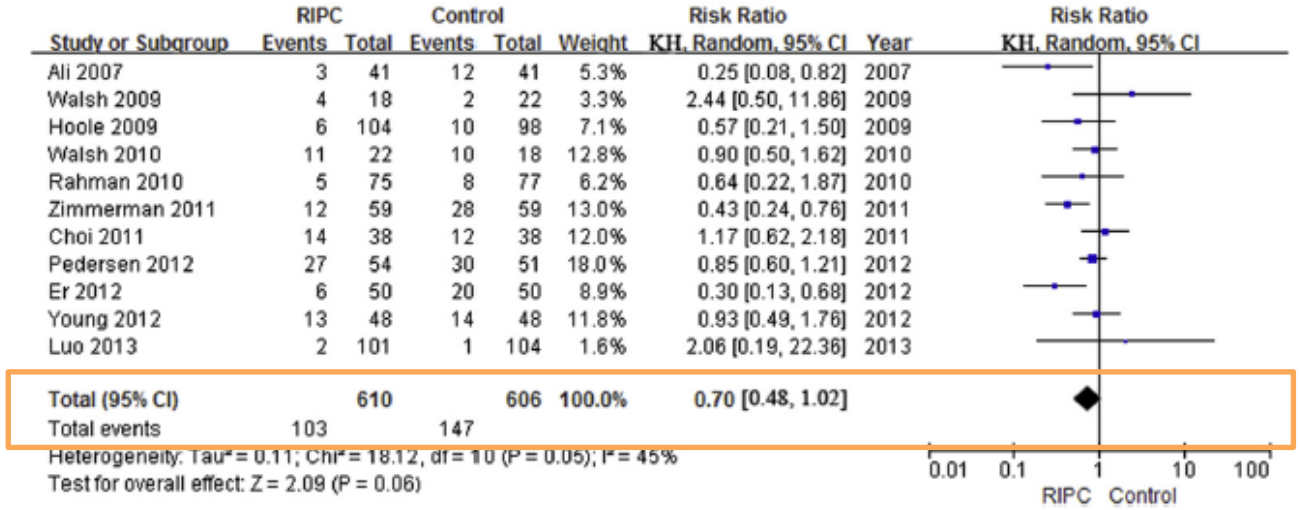


Figure 2. Comparison of remote ischemic preconditioning (RIPC) versus control group for the incidence of acute kidney injury (AKI). Abbreviations: CI, confidence interval; KH, Knapp-Hartung method.

Results:

- RIPC decreased the risk of AKI with marginal statistical
- There were no differences in postoperative kidney biomarkers (Cr, GFR), incidence of RRT, in-hospital mortality, hospital stay, or ICU stay

Conclusion:

- RIPC might be beneficial for the prevention of AKI following cardiac and vascular interventions, but the current evidence is not robust enough to make a recommendation.

Results were not that positive…
But until 2015..

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Remote Ischemic Preconditioning on Kidney Injury Among High-Risk Patients Undergoing Cardiac Surgery
A Randomized Clinical Trial

Alexander Zarbock, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Sven Martens, MD; Peter K. Zahn, MD; Britta Wolf, MD; Ulrich Goebel, MD; Christian I. Schwer, MD; Peter Rosenberger, MD; Helene Haeberle, MD; Dennis Görlich, PhD; John A. Kellum, MD; Melanie Meersch, MD; for the RenalRIPC Investigators

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189
Published online May 29, 2015.

Background

- Up to 30% develop AKI after cardiac surgery
- ~1% dependent on RRT

- Mechanism of AKI not fully understood, but injury to renal tubular epithelial cells is a universal aspect of the disease

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Objective and Study Design

- OBJECTIVE:
  - To determine whether RIPC reduces the rate and severity of AKI in patients undergoing cardiac surgery

- METHODS:
  - Multicenter, double-blind, RCT
  - Patients high risk for AKI undergoing cardiac surgery with cardiopulmonary bypass
  - Aug 2013 – June 2014
  - 240 patients from 4 hospitals in Germany

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

eTable S1: Cleveland Clinic Foundation Score according to Thakar et al. [1]

Risk Factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction < 35%	1
Preoperative use of Intra-aortic ballon pump (IABP)	2
Chronic obstructive Pulmonary Disease (COPD)	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only	1
Coronary Artery Bypass Grafting + valve surgery	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2)	2
Preoperative creatinine ≥2.1 /reference to 1.2)	5

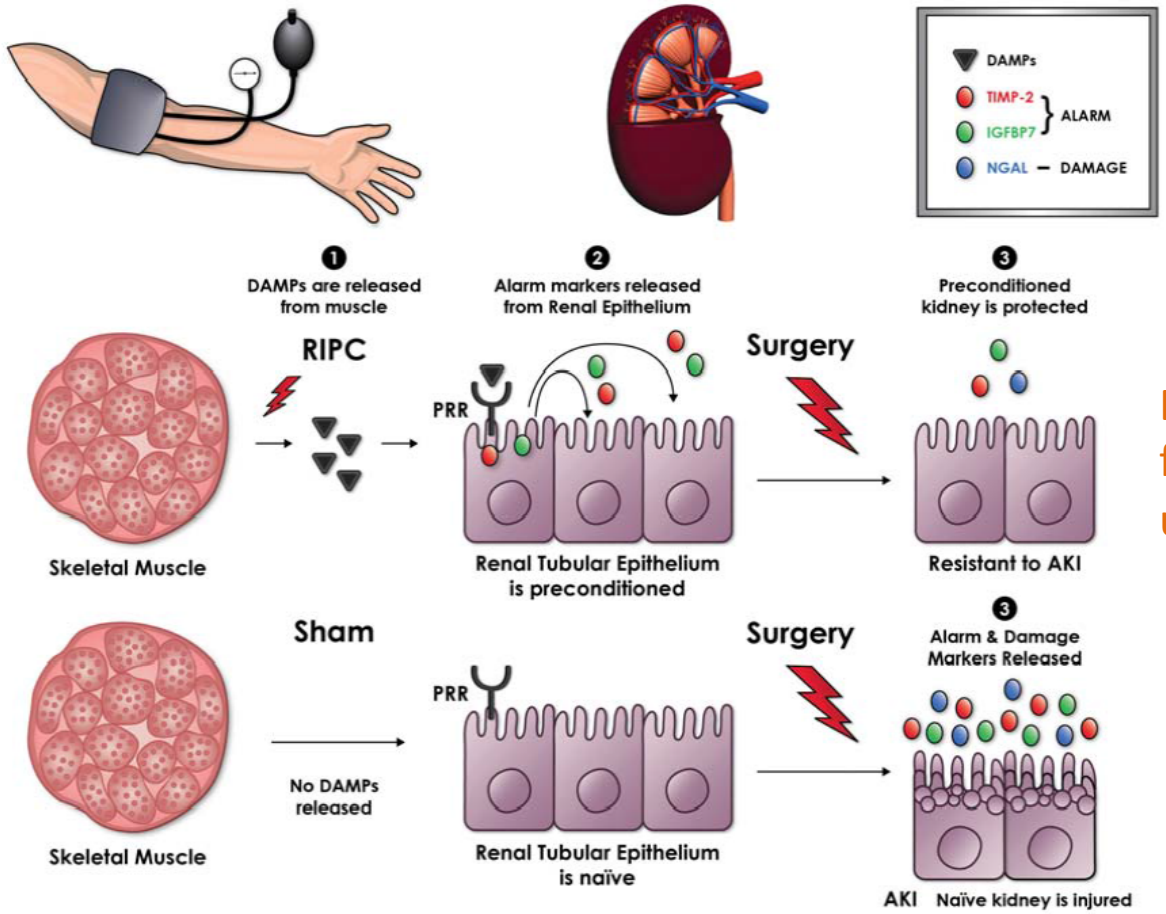
Exclusion criteria
- acute myocardial infarction ≤ 7 d
- age < 18 y
- off-pump heart surgery
- pre-existing AKI
- kidney transplantation
- CKD with eGFR < 30 ml/min
- pregnancy
- pAVK of upper limb
- hepatorenal syndrome
- sulfonamide and nicorandil

Score >= 6 : high risk patient, included into study

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Proposed mechanism

eFigure S3. - Proposed conceptual model for how RIPC results in fewer AKI events.



Down-regulate cell function and energy utilization

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

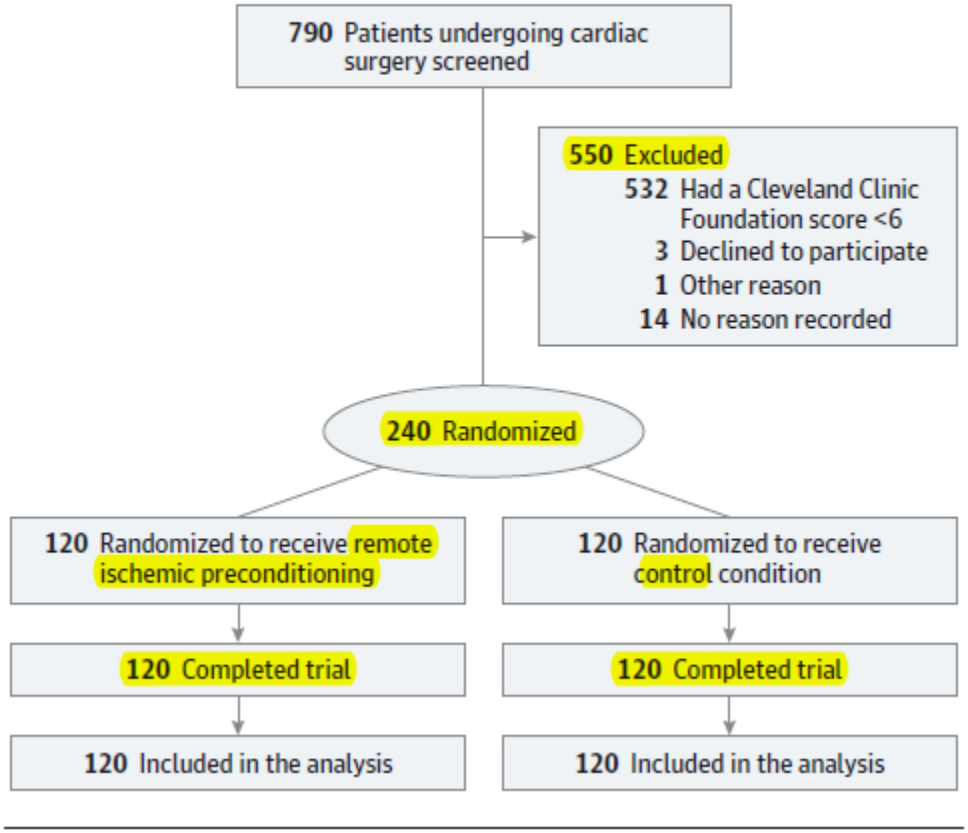
Randomization and Procedures

- Randomized on 1:1 basis
- Randomization codes were generated by computers and concealed
- Intervention provided by investigator not involving in care of patient
- Patients, anaesthesiologists, surgeons, ICU doctors all unaware of Tx assignment

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

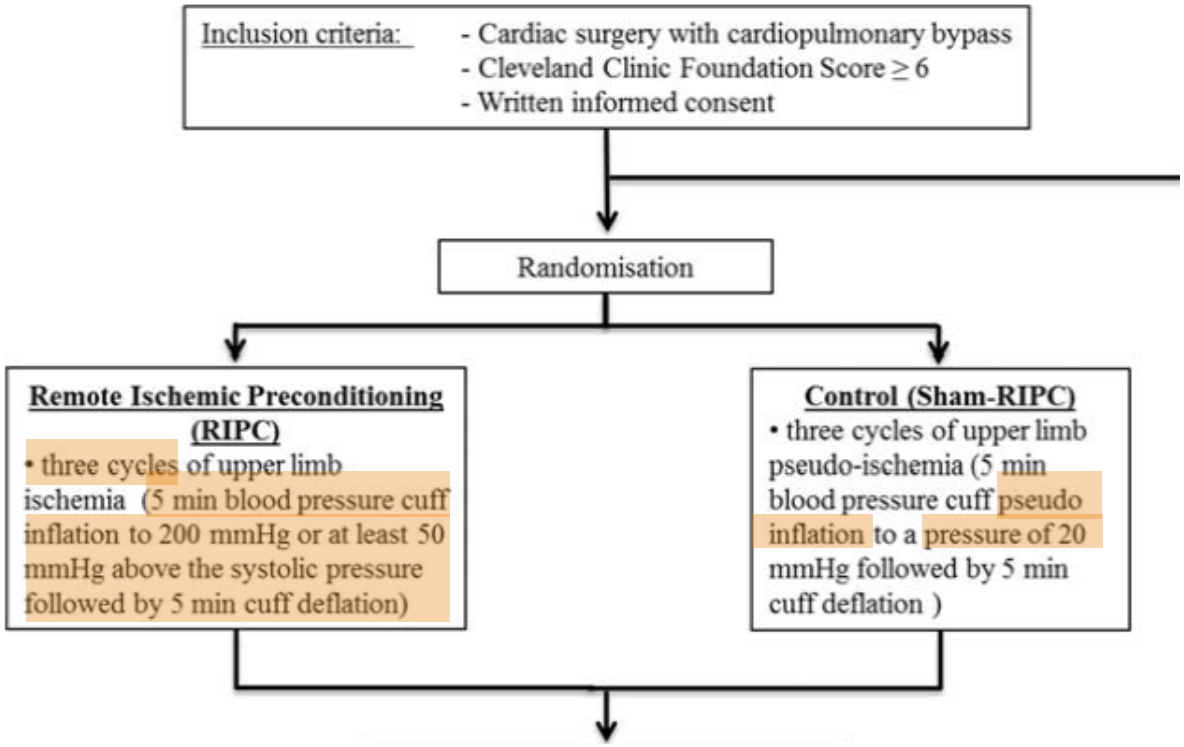
Randomization and Procedures

Figure 1. Participant Flow of Remote Ischemic Preconditioning in Patients Undergoing Cardiac Surgery



JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Randomization and Procedures



Anaesthesia maintained with volatile anaesthetics

Cardiopulmonary bypass:

- MAP 60-70 mmHg
- Non-pulsatile
- Hct 0.25 – 0.3
- Glucose < 200mg/dL

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Baseline

Table 1. Baseline and Operative Characteristics

	Control (n = 120)	RIPC (n = 120)
Age, mean (SD), y	70.6 (9.9)	70.1 (9.1)
Male sex, No. (%)	75 (62.5)	76 (63.3)
ASA grade, No. (%)[a]		
1	0	0
2	24 (20.0)	27 (22.5)
3	88 (73.3)	86 (71.7)
4	8 (6.7)	7 (5.8)
New York Heart Association class, No. (%)		
I	6 (5.4)	5 (4.5)
II	28 (25.0)	32 (28.8)
III	60 (53.6)	57 (51.4)
IV	18 (16.1)	17 (15.3)
Cleveland Clinic Foundation score, median (IQR), points[b]	6 (6-6)	6 (6-6)
Preoperative creatinine, mean (SD), mg/dL	1.2 (0.4)	1.1 (0.4)
eGFR, mean (SD), mL/min/1.73 m^2	56.4 (15.8)	56.7 (13.4)
Comorbidities, No. (%)		
Hypertension	116 (96.7)	116 (96.7)
Congestive heart failure	101 (84.2)	101 (84.2)
Diabetes	44 (36.7)	46 (38.3)
Chronic obstructive pulmonary disease	40 (33.3)	36 (30.0)
Chronic kidney disease	39 (32.5)	35 (29.2)
Previous heart surgery	14 (11.7)	13 (10.8)
Left ventricular ejection fraction <35%	13 (10.8)	23 (19.2)

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Baseline

Medication, No. (%)		
Aspirin	66 (55.0)	77 (64.2)
Clopidogrel	15 (12.5)	11 (9.2)
β-Blockers	78 (65.0)	68 (56.7)
Statins	85 (70.8)	80 (66.7)
Diuretics	71 (59.2)	63 (52.5)
ACE inhibitors or ARBs	73 (60.8)	71 (59.2)
Intraoperative times, median (IQR), min		
Aortic cross-clamp	78.0 (58.5-112.0)	86.0 (65.0-105.0)
Cardiopulmonary bypass	116.0 (89.5-165.0)	120.0 (99.5-150.0)
Procedure, No. (%)		
CABG only	36 (30.0)	44 (36.7)
Valve only	21 (17.5)	28 (23.3)
Combined or other	63 (52.5)	48 (40.0)
Baseline urine biomarkers, median (IQR)		
Urine (TIMP-2) × (IGFBP7), ng/mL^2/1000	0.2 (0.1-0.5)	0.3 (0.1-0.7)
Urine NGAL, ng/mL	10.7 (4.5-30.5)	9.9 (4.9-25.2)
Urine HMGB-1, ng/mL	0 (0-0)	0 (0.0-20.5)
(TIMP-2) × (IGFBP7) ≥0.5, No. (%)	31 (26.3)	40 (33.6)

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Outcomes

- Primary endpoint
  - Occurrence of AKI within first 72 hours after surgery
  - Define according to KDIGO guideline

- Secondary endpoint
  - Severe acute kidney injury (stage 2-3) within 72 hours
  - 30-day all-cause mortality
  - Need for RRT
  - Duration of ventilator support
  - Length of ICU and hospital stay
  - In-hospital death
  - Concentrations of various urinary biomarkers in the first 24
  - Perioperative MI and stroke

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Calculation

- Estimated sample size:
  - Expected AKI rate in control : 50%
  - Expected absolute risk reduction : 18%
  - Power: 80%
  - Calculated sample size per treatment group: 117 patients

- 240 patients recruited in the study
- Follow intention- to- treat principle

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

The Biomarkers

- Blood and urine sampled:
  - Before and immediately after RIPC
  - At 4, 12, 24 hours after surgery

- Insulinlike growth factor–binding protein 7 **(IGFBP7)**
- Tissue inhibitor of metalloproteinases 2 **(TIMP-2)**
- Inducers of G1 cell cycle arrest
- Predict AKI
- ***ALARM MARKER***

- Urine neutrophil gelatinase–associated lipocalin **(NGAL)**
- Released after kidney injury
- ***DAMAGE MARKER***

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Results – Primary and Secondary Outcome

Table 2. Primary and Secondary Study Outcomes, by Group

	Control (n = 120)	RIPC (n = 120)	ARR or Median Difference (95% CI)	*P* Value
Primary Outcome, No. (%)				
AKI within 72 h	63 (52.5)	45 (37.5)	15 (2.56 to 27.44)	.02
AKI stage				
1	32 (26.7)	30 (25)		
2	14 (11.7)	8 (6.7)		
3	17 (14.2)	7 (5.8)		
Secondary Outcomes				
RRT, No. (%)	19 (15.8)	7 (5.8)	10 (2.25 to 17.75)	.01
Mechanical ventilation, median (IQR), h	15 (12-21)	14 (11-21)	1 (−1.54 to 4)[a]	.16
Intensive care unit stay, median (IQR), d	4 (2-7)	3 (2-5)	1 (0 to 2)[a]	.04
Hospital stay, median (IQR), d	13 (10-19)	12 (9-19)	1 (−2 to 2.5)[a]	.45
In-hospital death, No. (%)	4 (3.3)	6 (5.0)	1.67 (0 to 6.72)[b]	.54
30-d mortality, No. (%)	5 (4.2)	7 (5.8)	1.67 (0 to 7.18)[b]	.77
Myocardial infarction, No. (%)	5 (4.2)	6 (5.0)	0.83 (0 to 6.12)[b]	.76
Stroke, No. (%)	3 (2.5)	2 (1.7)	0.83 (0 to 4.45)[b]	.65

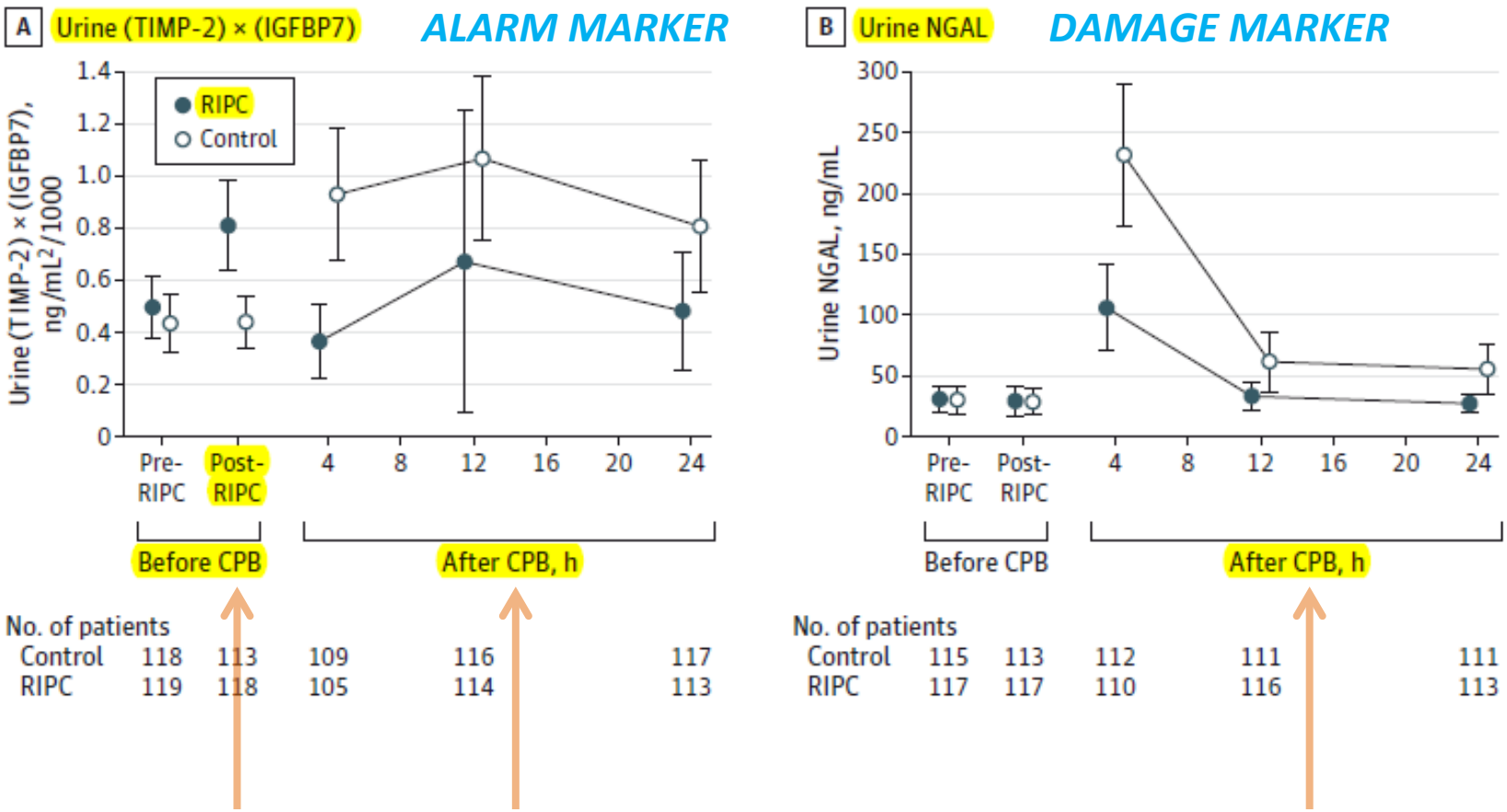
: KDIGO criteria according the KDIGO guidelines [2]

Serum creatinine	Urine output
1.5-1.9 times baseline OR ≥ 0.3 mg/dl increase	< 0.5 ml/kg/h for 6-12 hour
2.0-2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hour
3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl OR Initiation of renal replacement therapy	< 0.3 ml/kg/h for ≥ 24 hour OR Anuria for ≥ 12 hours

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Results – Biomarkers

Figure 2. Analysis of Acute Kidney Injury Biomarkers



JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Discussion

- RIPC lowers rate of AKI, RRT, ICU stay after cardiac bypass surgery

- Pathophysiology of AKI and exact protective mechanism cannot be proven yet
- RIPC may release mediators inducing G1 cell-cycle arrest
- The short period of G1 cell-cycle arrest protects the kidney until insults have passed

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

Discussion

- If to calculate 30-days mortality results
- With a power of 80%
- Would need > 4000 patients (183 deaths) to detect a difference of mortality

JAMA. 2015;313(21):2133-2141. doi:10.1001/jama.2015.4189

How about RIPC in AAA repair ?

Results not always positive …

** For AAA repair in open approach**

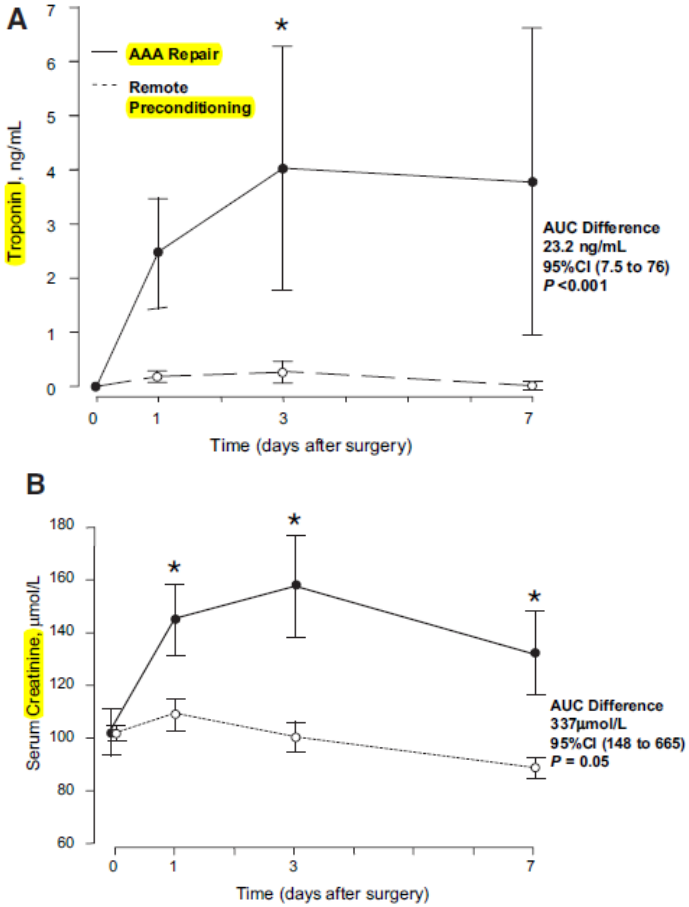
Remote Ischemic Preconditioning Reduces Myocardial and Renal Injury After Elective Abdominal Aortic Aneurysm Repair

Circulation. 2007;116

A Randomized Controlled Trial

TABLE 3. Major Adverse Outcomes After Open AAA Repair

	Remote Preconditioning	Conventional AAA Repair	*P*
Sample size	41	41	
In-hospital			
Myocardial injury, no. (%)	5 (12)	16 (39)	0.005
Myocardial infarction, no. (%)	2 (5)	11 (27)	0.006
Renal impairment, no. (%)	3 (7)	12 (30)	0.009
In-hospital death, no. (%)	2 (5)	3 (7)	0.77



Conclusions—In patients undergoing elective open abdominal aortic aneurysm repair, RIPC reduces the incidence of postoperative myocardial injury, myocardial infarction, and renal impairment. (*Circulation*. 2007;116[suppl I]:I-98–

Remote Ischemic Preconditioning Does Not Affect the Incidence of Acute Kidney Injury After Elective Abdominal Aortic Aneurysm Repair

Noelle Murphy, MB, BCh, BAO,* Ajith Vijayan, MB, BCh, BAO,‖ Stephen Frohlich, MB, BCh, BAO,*
Frank O'Farrell,† Mary Barry, MB, BCh, BAO,‡ Stephen Sheehan, MB, BCh, BAO,‡
John Boylan, MB, BCh, BAO,§ and Niamh Conlon, MB, BCh, BAO§

Journal of Cardiothoracic and Vascular Anesthesia, Vol 28, No 5 (October), 2014: pp 1285–1292

Randomised 62 patients in 1:1 ratio
3 cycles 5-mins arm ischemia

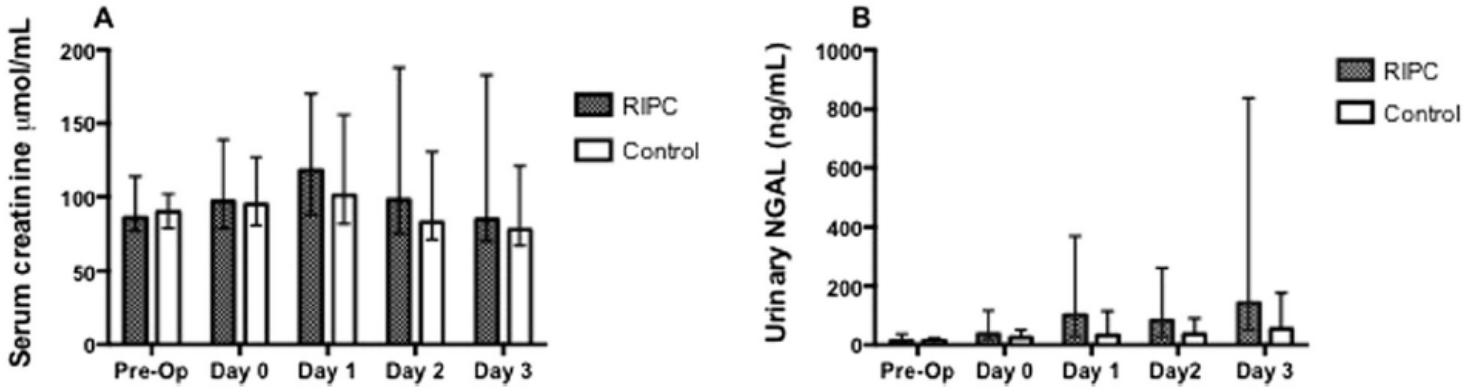


Fig 2. Biomarkers of renal injury up to postoperative day 3. (A) Median serum creatinine (µmol/mL) and (B) median urinary NGAL ng/mL.

Table 5. Postoperative Cardiac Events

	RIPC	Control	p Value
New troponin elevation, no. (%)	16 (51%)	9 (29%)	0.11
Myocardial infarction, no. (%)	4 (13%)	2 (6%)	0.67
New arrhythmia, no. (%)	5 (16%)	1 (3%)	0.2
Postoperative vasopressors Requirement no. (%)	14 (45%)	11 (35%)	0.61

Conclusion: **RIPC did not reduce the risk of postoperative renal failure or myocardial injury in patients undergoing open AAA repair. The authors' results do not support the introduction of this technique to routine clinical practice.**

How about in EVAR ??

I can only find one study between AKI and EVAR AAA..

RIPC in AAA repair

RESEARCH Open Access

Remote ischaemic preconditioning versus sham procedure for abdominal aortic aneurysm repair: an external feasibility randomized controlled trial

Ronelle Mouton[1*], Jon Pollock[2], Jasmeet Soar[1], David C. Mitchell[3] and Chris A. Rogers[4]

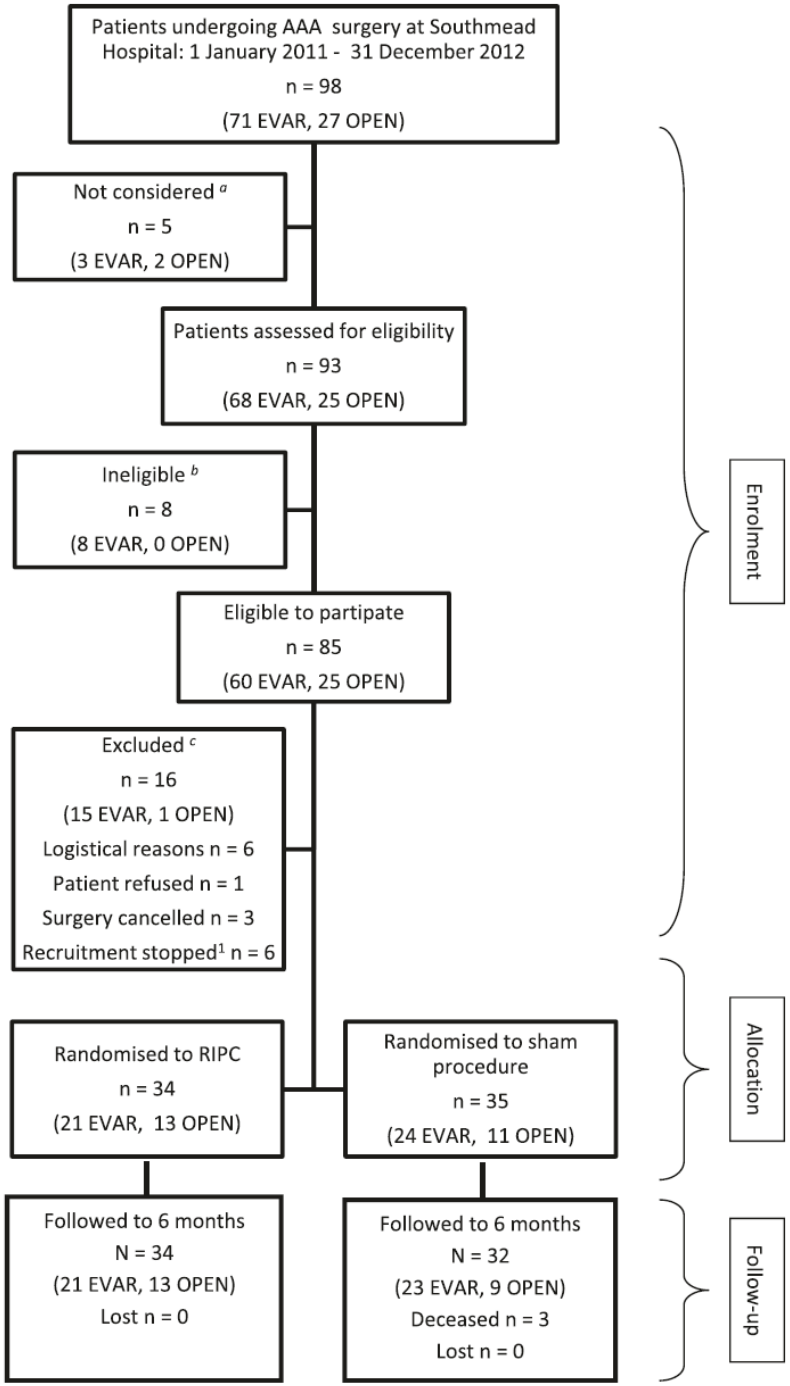
Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3

RIPC in AAA repair

- In UK, prevalence of AAA id 5-7% in men aged 65-74
- At risk of perioperative MI and renal impairment

- A pilot study
  - To investigate whether RIC could be successfully introduced in elective AAA repair
  - To obtain information to design a multi-center RCT

Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3



RIPC in AAA repair

- UK single large city hospital
- EVAR or open approach
- 2010 - 2012

Study group:

- 3 cycles
- 5 mins arm ischemia (cuff inflated 40mmHg above SBP)
- 5 mins reperfusion

Control group:

- Cuff inflated to 40mmHg only

- Except anesthetists
- All others were blinded

Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3

RIPC in AAA repair - baseline

Table 1 Baseline patient characteristics

	Randomised allocation	
	RIC (n = 34)	SHAM (n = 35)
Age (years)	72 (6)	72 (7)
Creatinine (μmol/L)	102 (52)	91 (19)
Urea (mmol/L)	7 (4)	6 (2)
Hb (g/dL)	14 (2)	14 (2)
Albumin (g/L)	37 (5)	37 (4)
Anaerobic threshold (ml/kg/min)	12 (2)	13 (2)
VO_2 max (ml/kg/min)	14 (3)	17 (6)
VE/VCO_2 (l/l)	33 (6)	31 (4)
V-POSSUM	19 (4)	19 (4)
ACEI	20 (59 %)	17 (49 %)
Statin	26 (77 %)	25 (71 %)
Beta-blocker	12 (35 %)	11 (31 %)
Hypertension	26 (77 %)	25 (71 %)
Ischaemic heart disease	13 (38 %)	9 (26 %)
Cerebrovascular disease	6 (18 %)	7 (20 %)
Congestive cardiac failure	5 (15 %)	1 (3 %)
Predicted complex EVAR	10 (29 %)	1 (3 %)

Table 2 Operative characteristics

	Randomised allocation	
	RIC (n = 34)	SHAM (n = 35)
Procedure time (hours)		
EVAR	2.96 (0.86)	2.28 (0.45)
Open	4.07 (0.22)	4.87 (0.73)
Anaesthetic time (hours)		
EVAR	0.71 (0.05)	0.64 (0.04)
Open	1.16 (0.10)	1.36 (0.23)

Data are shown as mean (SD)

In RIC group, more :

- history of IHD
- CHF
- Predicted complex EVAR procedure (anatomical difficulties)

- Reflected in longer OT time in RIC EVAR group

Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3

RIPC in AAA repair - results

Table 3 Clinical Outcomes

	Randomised allocation	
	RIC (n = 34)	SHAM (n = 35)
Acute kidney injury		
AKIN 1	9 (27 %)	7 (20 %)
AKIN 2	7 (21 %)	3 (9 %)
AKIN 3	0 (0 %)	2 (6 %)
Myocardial Infarction	5 (15 %)	2 (6 %)
New post-op ECG changes	7(20 %)	7 (20 %)
New arrhythmia	7 (21 %)	5 (14 %)
Troponin T > 14 ng/L	16 (47 %)	10 (29 %)
Other post-operative issues[a]	13 (38 %)	12 (34 %)
Death	0 (0 %)	3 (9 %)

- AKI and MI more in RIC group
- BUT, Ix showed ↑complication was related to predicted complexity of EVAR

	Complex EVAR (11)	Non complex EVAR/ open (57)
AKI	6	22
MI	3	4

Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3

RIPC in AAA repair - results

Participant and staff interviews

scrub and theatre staff. From the staff interview questions, 86 % indicated no or minimal effect of the intervention on day-to-day practice, 11 % reported a small effect or minor point, and 1 % a moderate effect or significant point. The surgeons and radiologist all universally rated the intervention as having minimal impact on normal work patterns.

average 50 min longer. The randomization scheme for an adequately powered definite RCT should take into account surgical procedure, surgical complexity and participant risk, to avoid the imbalance between groups in these potential confounders, as was observed in this study.

Mouton *et al. Trials* (2015) 16:377
DOI 10.1186/s13063-015-0899-3

You may question CIN may also take into account of AKI …

RIPC & Contrast Induced Nephropathy (CIN)

Eur J Vasc Endovasc Surg (2015) ■, 1—6

Remote Ischemic Preconditioning To Reduce Contrast-Induced Nephropathy: A Randomized Controlled Trial

T.P. Menting [a], T.B. Sterenborg [a], Y. de Waal [b], R. Donders [c], K.E. L.J. SchultzeKool [e], M.C. Warlé [a,*]

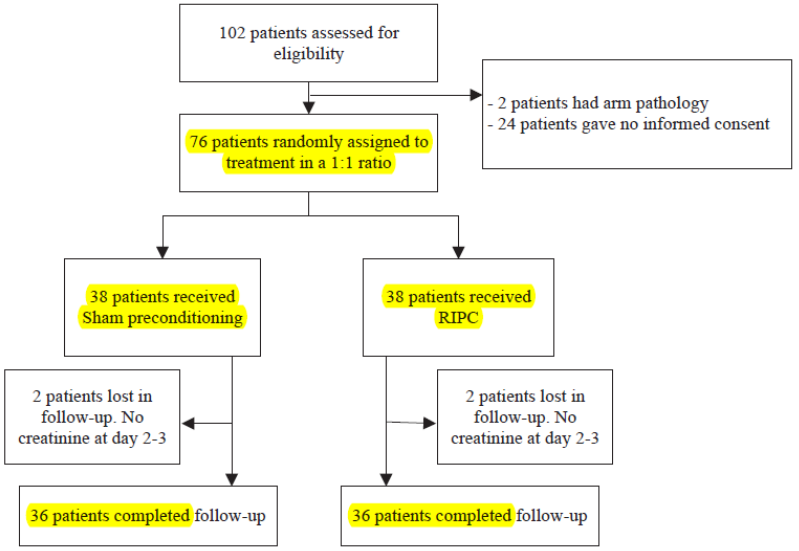


Figure 1. Study flow chart.

Methods: The RIPCIN study is a multicenter, single blinded, randomized controlled trial in which 76 patients at risk of CIN received standard hydration combined with RIPC or hydration with sham preconditioning. RIPC was applied by four cycles of 5 min ischemia and 5 min reperfusion of the forearm. The primary outcome measure was the change in serum creatinine from baseline to 48 to 72 hours after contrast administration.

RIPC & CIN

Table 3. Trial outcomes.

	Sham group ($n = 36$)	RIPC group ($n = 36$)	p
Primary endpoint			
Change in serum creatinine from baseline to 48–72 hr, µmol/L	−0.3 ± 14.7	0.25 ± 14.6	.87
Secondary endpoints			
Change in serum creatinine from baseline to 4–6 hr, µmol/L	−14.5 ± 11.8	−11.4 ± 11.0	.26
Contrast induced nephropathy, n (%)	2 (6)	2 (6)	1.00
Re-hospitalization within 6 wk	0 (0)	0 (0)	n.a.
Dialysis within 6 wk	0 (0)	0 (0)	n.a.
Mortality within 6 wk	2 (6)	0 (0)	0.49

Data given in mean ± SD, n (%).
RIPC = remote ischaemic preconditioning; wk = weeks.

Table 4. Change in serum creatinine per group divided by Mehran risk score.

Mehran risk score	n	Group	Change in serum creatinine (mean ± SD)	p
<5	32	Sham ($n = 15$)	−0.2 ± 14.2	
		RIPC ($n = 17$)	0.9 ± 13.1	.83
6–10	29	Sham ($n = 16$)	−6.1 ± 8.2	
		RIPC ($n = 13$)	1.1 ± 18.6	.18
≥11	11	Sham ($n = 5$)	17.8 ± 20.1	
		RIPC ($n = 6$)	−3.3 ± 9.8	.048

RIPC = remote ischaemic preconditioning.

Conclusion: RIPC, as an adjunct to standard preventive measures, does not improve serum creatinine levels after contrast administration in patients at risk of CIN according to the Dutch guideline. However, the present data indicate that RIPC might have beneficial effects in patients at a high or very high risk of CIN (Mehran score ≥ 11).

How to perform RIPC?

Table 3
Characteristics of included trials on cardiac surgery.

Author year participant number (RIPC:Control)	Significant primary outcome result in favour of RIPC	Type of surgery	Site and method of applying of the ischaemia/reperfusion stimulus	Timing of the stimulus in relation to anaesthetic and surgery	Use of volatile anaesthetic agents
Hausenloy [21] 2007 27/30	Yes	Elective CABG on CPB	Upper limb 3 × 5min cycles	After induction of anaesthesia and before surgery.	No volatile agents.
Venugopal [22] 2009 23/22	Yes	Elective CABG on CPB	Upper limb 3 × 5 min cycles	After induction of anaesthesia and before surgery.	17/22 in control group and 17/23 in RIPC group had inhalational anaesthesia.
Ali N [24] 2010 50/50	Yes	Elective CABG on CPB	Upper limb 3 × 5 min cycles.	After induction of anaesthesia and before extracorporeal bypass.	General anaesthesia. No further details stated.
Li Cardiac [25] 26/27 2010	No	Valve replacement on CPB	Lower limb 3 × 4 min cycles	After induction of anaesthesia. Time in relation to surgery commencement not stated.	Isoflurane used for maintenance
Rahman [29] 2010 80/82	No	Elective and emergency CABG on CPB	Upper limb 3 × 5 min cycles	After induction of anaesthesia. Time in relation to surgery commencement not stated.	Enflurane or sevoflurane maintenance while on CPB.
Hong [30] 2010 65/65	No	Elective CABG without CPB	Upper limb 4 × 5 min cycles	After induction of anaesthesia with surgery proceeding.	Maintenance with sevoflurane.
Choi [31] 2011 38/38	No	Elective valve surgery under CPB	Lower limb 3 × 10 min cycles	After induction of anaesthesia and at least 10 min before CPB.	Maintenance with sevoflurane.
Zimmerman [32] 2011 60/60	Yes	Elective CABG +/− aortic valve surgery with CPB	Lower limb 3 × 5 min cycles	After induction of anaesthesia and at least 10 min before CPB.	Maintenance with isoflurane.
Karupassamy [33] 2011 27/27	No	Elective CABG surgery with CPB	Upper limb 3 × 5 min cycles	After induction of anaesthesia. Time in relation to surgery commencement not stated.	Maintenance with isoflurane until CPB.
Wu [34] 2011 25/25	No	Mitral valve replacement with CPB.	Upper limb 3 × 5 min cycles. This trial had 3 arms and as summary outcome data only were provided, we excluded the lower limb RIPC group.	After induction of anaesthesia and before surgery.	No volatile agents
Young [35] 2012 48/48	No	Elective CABG +/− valve surgery	Upper limb 3 × 5 min cycles	After induction and beginning at first incision.	All had maintenance with propofol and isoflurane.

Table 3. Details of RIPC Trials Using Tourniquet Cuff Around Limb

Reference	Limb Used for RIPC	No. of Limbs Used for RIPC	Ischemia/Reperfusion Interval (min)	Total Ischemia Duration (min)
Walsh et al[18] (2009)	Lower limb	2	10	20
Hoole et al[19] (2009)	Nondominant upper arm	1	5	15
Rahman et al[20] (2010)	Left upper arm	1	5	15
Thielmann et al[21] (2010)	Left upper arm	1	5	15
Zimmerman et al[23] (2011)	Lower limb	1	5	15
Choi et al[24] (2011)	Lower limb	1	10	30
Er et al[25] (2012)	Upper arm	1	5	20
Young et al[26] (2012)	Upper arm	1	5	15
Pedersen et al[27] (2012)	Lower limb	1	5	20
Lucchinetti et al[28] (2012)	Lower limb	1	5	20
Luo et al[29] (2013)	Upper arm	1	5	15

Abbreviation: RIPC, remote ischemic preconditioning.

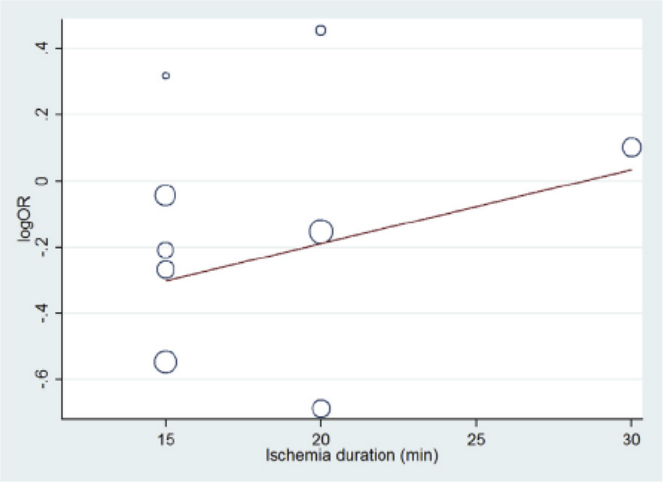


Figure 6. Metaregression analysis indicated there was no dose effect of remote ischemic preconditioning using tourniquet cuff around the limb for acute kidney injury prevention based on different ischemia durations (coefficient = 0.08; 95% confidence interval, −0.74 to 0.90; $P = 0.8$).

No consensus on exact method

But usually:

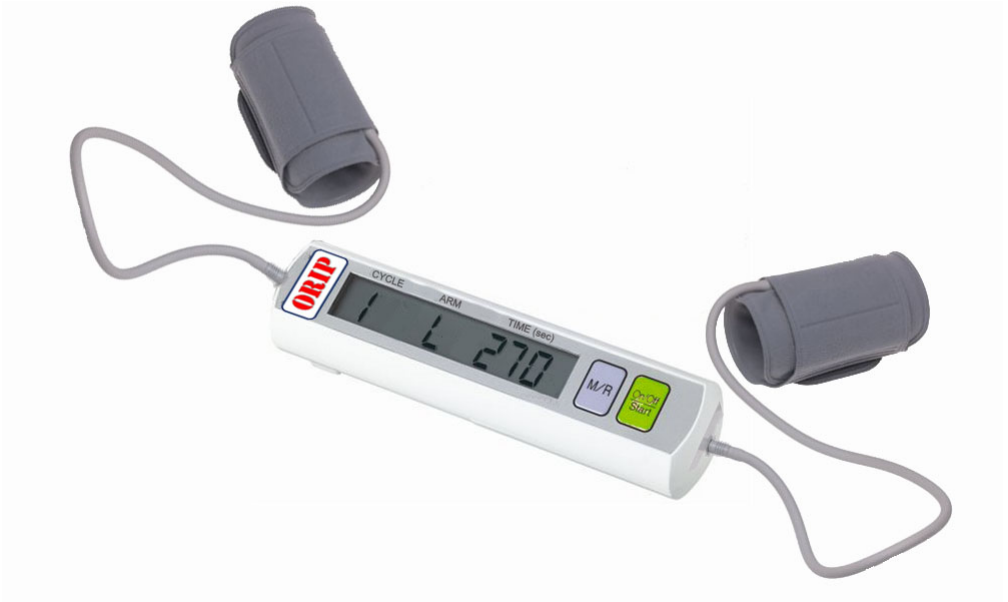
- After induction of anaesthesia, before surgery

- 3-4 cycles 5 mins ischemia-reperfusion
- Upper arm
- 40-50mmHg above SBP or at 200mmHg

- No dose-effect relationship

Am J Kidney Dis. 64(4):574-583.

Simple sphygmometer



Electronic device for RIPC

Conclusion

- Remote ischemic preconditioning (RIPC)
  - Easy
  - Non-invasive
  - Cost – effetive
  - Simple

- Growing evidence to show its effectives in reducing post op AKI, RRT, MI, ICU stay in major cardiovascular surgery
- Study on its use in AAA EVAR repair is currently limited by the complexity of EVAR procedure
- May also have beneficial effect in patients with high or very high risk of CIN