DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF CAPE TOWN AND GROOTE SCHUUR HOSPITAL, AND THE HATTER INSTITUTE FOR CARDIOVASCULAR RESEARCH, UNIVERSITY OF CAPE TOWN MEDICAL SCHOOL, OBSERVATORY, CAPE TOWN.

TIME IS MUSCLE: A SYSTEMATIC REVIEW INVESTIGATING THE ROLE OF REMOTE ISCHAEMIC PRECONDITIONING AND GLUCOSE-INSULIN-POTASSIUM INFUSIONS AS ADJUNCTIVE THERAPIES TO REVASCULARISATION IN CORONARY ARTERY DISEASE

by

Shikar Mothilal, MBChB. FCP

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Faculty of Health Sciences

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Supervisors: **Lionel H Opie, Hatter Institute for Cardiovascular Research**

Mark Engel, University of Cape Town

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DECLARATION PAGE

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TIME IS MUSCLE: A SYSTEMATIC REVIEW INVESTIGATING THE ROLE OF REMOTE ISCHAEMIC PRECONDITIONING AND GLUCOSE-INSULIN-POTASSIUM INFUSIONS AS ADJUNCTIVE THERAPIES TO REVASCULARISATION IN CORONARY ARTERY DISEASE

Shikar Mothilal[1], Lionel H Opie[2], Mark Engel[1]

1. University of Cape Town, Groote Schuur Hospital
2. Hatter Institute for Cardiovascular Research

ABSTRACT: In the management of coronary artery disease (CAD) most advances have concerned improvements in catheter-based interventional techniques and complex pharmacotherapy, with an emphasis on time, which unfortunately, cannot always achieved. However, simple measures with reassuring benefit that can be performed even by non-cardiologists have been largely overlooked, or understated. These include limiting reperfusion injury by remote ischaemic conditioning (RIPC), a powerful protective mechanism that can be elicited by the transient occlusion of blood flow to a limb with a blood pressure cuff. More controversially, glucose-insulin-potassium (GIK) therapy in early ST elevation myocardial infarction (STEMI) has the potential to improve outcomes especially when timely restoration of vessel patency is difficult to achieve. This systematic review will evaluate the role of these therapies as adjuncts to revascularisation for treating coronary artery disease either electively or during an acute coronary syndrome.

Objectives: To determine if RIPC or GIK therapy for CAD leads to reduced mortality (primary objective), infarct size, cardiac enzyme release or major adverse cardiac and cerebral events (MACCE) and to identify adverse effects associated with RIPC or GIK (secondary objectives).

Methods: The search strategy identified 100 articles from 2 databases, Cochrane and PubMed. Following review of the titles, 85 articles were excluded, leaving 15 studies for full-text review of which 6 articles were included in the final subset.

Results: RIPC as part of adjunctive therapy for patients undergoing revascularisation for coronary artery disease leads to reduced mortality, cardiac enzyme release and improved myocardial salvage compared to placebo. Early GIK therapy in STEMI leads to decreased in-

hospital mortality, left ventricular infarct size and composite end point of cardiac arrest, 30-day mortality and heart failure compared to placebo.

Conclusions: RIPC and GIK are valuable adjunctive therapies for patients undergoing revascularisation for coronary artery disease. More large scale, multi-centred, placebo controlled randomised controlled trials are needed to evaluate this further.

INTRODUCTION

Coronary artery disease (CAD) is among the leading causes of mortality worldwide contributing to at least 3 million deaths per year.[1] From being an illness seen predominantly in the developed world it has become increasingly common in developing countries where progressive urbanisation has led to a scourge of lifestyle diseases and consequently, risk factors for coronary artery disease.[2] In South Africa, coronary artery disease is the second leading cause of death contributing to more than 10% of total deaths per year.[2]

The spectrum of coronary artery disease ranges from chronic stable angina to the acute coronary syndromes, namely unstable angina, non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI).[3] Of these, STEMI portends the most severe short term prognosis as it implies complete occlusion of a coronary artery which ultimately leads to myocardial necrosis.[4] The timely revascularisation of an occluded vessel is therefore a key component of therapy.[5,6] This can be achieved by thrombolysis or coronary angiography. In South Africa and other developing countries where resources are scarce, delays to achieve definitive revascularisation plague the health care system and angiographic facilities are not easily accessible, the role of adjunctive strategies to improve outcomes while still being easy to perform, safe and cost effective become especially important. Furthermore, revascularisation itself carries a risk of reperfusion injury due to the abrupt restoration of blood flow to previously ischaemic myocardium.[7]

Of the extensive list of potentially cardio-protective adjunctive strategies, other than standard pharmacotherapy, that target the biochemical pathways involved in CAD and reperfusion injury many have yielded consistently negative results (Table 1).[8] This study however will evaluate remote ischemic conditioning and glucose-insulin-potassium therapy in further detail.

Table 1. TESTED CARDIOPROTECTIVE STRATEGIES IN ACS[8]	**Outcome**
Conditioning (pre/post)	Positive
Glucose-insulin-potassium	Positive
Cyclosporine	Doubtful
Adenosine	Doubtful
Corticosteroids	Negative
Erythropoietin	Negative
Recombinant superoxide dismutase	Negative
Prostacyclin	Negative
Hyaluronidase	Negative
Magnesium	Negative
Anti-leucocyte interventions (anti-CD18 monoclonal antibodies)	Negative

* This table excludes standard pharmacotherapy for ACS such thrombolytic therapies, anticoagulation, antiplatelet agents, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers etc.

Reperfusion injury and ischaemic preconditioning

Revascularisation of an occluded coronary artery is an important target for therapy in STEMI.[5,6] Recent emphasis has been on achieving the shortest door to needle or balloon times but this has proven difficult to attain in developed, and more so, in developing countries.[1,2,9] Furthermore, there has been growing evidence to suggest that recanalisation of an occluded artery is an important contributor to myocardial damage accounting for up to 50% of the final infarct size.[7] This effect is termed "ischaemic reperfusion injury" which refers to the paradoxical myocardial, vascular or electrophysiological dysfunction that is induced by the restoration of blood flow to previously ischaemic tissue. It is seen in many organs and has been demonstrated in both animal and human models.[10] Reperfusion injury in the heart may be manifest by reperfusion arrhythmias, endothelial damage with microvascular dysfunction, myocardial stunning and worsening myocardial infarction.[11] The mechanism, although not well defined, is thought to be contributed to by oxidative stress from an abrupt re-oxygenation of ischaemic tissue as well as intracellular calcium overload & acid-base disturbances.[11]

Ischaemic preconditioning, on the other hand, is an intervention that attempts to reduce the potentially negative sequelae associated with reperfusion by intentionally evoking brief periods of ischaemia. It is applied either locally to coronary vasculature with catheter balloon inflations or in a much more simple manner "remotely" with cycles of blood pressure cuff inflations to about 200mmHg for 5 minutes before the anticipated reperfusion. The latter is therefore termed remote ischaemic preconditioning (RIPC). The precise nature of the transducing signal from remote tissue to target organ is unclear, however, humoral or neuronal response mechanisms have largely been implicated.[12] In animal studies adenosine, bradykinin and calcitonin gene related peptide have been identified as important mediators in this neurohormonal stimulus.[13]

Another proposed, although less well established theory, is the induction of counter-regulatory kinases via the reperfusion injury salvage kinase (RISK) and the survival activator enhancement pathway (SAFE) pathways in multiple organs.[14,15] The cytokine tumor necrosis factor alpha (TNFα) plays a crucial role in this process. Although TNFα is thought to contribute to myocardial dysfunction in ischaemia and heart failure it paradoxically initiates the activation of these pathways, which serve to enhance mitochondrial stability by opening ATP dependent potassium channels & by closing mitochondrial permeability

transition pores.[15] This is a critical step in preventing ATP depletion and cardiomyocyte death during reperfusion (Figure 1).

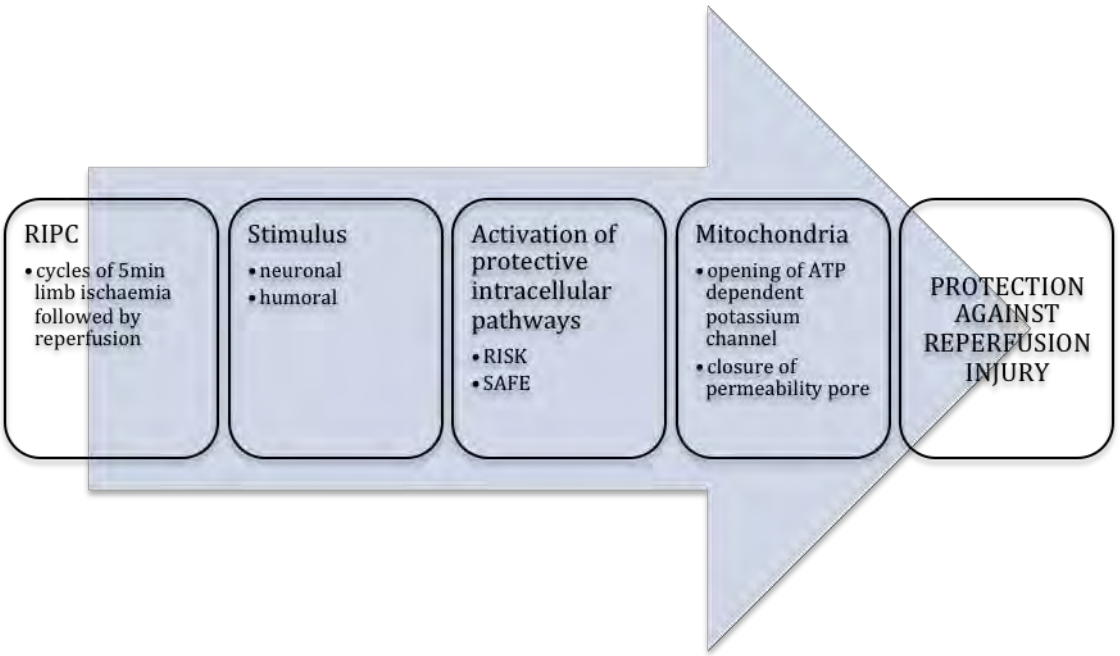


Figure 1. Mechanism of remote ischaemic conditioning (RIPC)

RISK indicates reperfusion injury salvage kinase; SAFE, survival activator enhancement; ATP, adenosine triphosphate. The cytokine tumor necrosis factor alpha (TNFα) plays a critical role in activation of these protective pathways.

Reperfusion injury and glucose-insulin-potassium therapy

Glucose-insulin-potassium (GIK) administered at the time of infarction has attracted interest after being introduced by Sodi-Pallares in 1962 when it was used primarily as a polarising solution to stabilise myocyte membranes and correct ECG abnormalities.[16] The implications were unclear as to the potential long-term effect of GIK however in the single patient who was treated early in the Sodi-Pallares study, there was electrocardiographic improvement suggesting a therapeutic benefit for GIK.

Opie observed that high FFA levels adversely affected cardiac rhythm and function.[17] He explained that the metabolic damage during acute myocardial infarction was caused by high levels of circulating fatty acids (FFAs) which were elevated as a result of the release of counter-regulatory catecholamines and cytokines, which stimulate lipolysis.[18] He thereafter expanded the concept by delineating the effect of suppressing high FFA levels and the major pathways in which GIK could be metabolically protective.[19]

Although lower levels of FFA are an important myocardial fuel in the fasted state, abnormally high FFA levels were demonstrated by Mjos in 1971 to be harmful because their metabolism led to myocardial oxygen wastage.[20] Fatty acid intermediates inhibited glycolysis and led to higher levels of lactate as well as hydrogen ions, which reduce cardiac contractility, lead to diastolic dysfunction and potentiate arrhythmias.[21,22]

The rationale for GIK would be ultimately to reduce circulating FFAs and thereby attenuate their deleterious metabolic effects.[23,24] GIK has been shown to enhance glycolytic flux within cells and increase ATP production, which maintains membrane pump and ion homeostasis.[25] This leads to greater contractile function and cellular viability of the myocyte.[26] Insulin, a key component of GIK, suppresses lipase and intracellular cAMP in adipose tissues thereby disrupting the B-adrenergic signaling during catecholamine-mediated lipolysis (Figure 2).[27] It helps correct the untoward effect of hyperglycaemia, a consequence of the acute catecholamine elevation in AMI, which potentiates abnormal vascular responsiveness, thrombus formation and platelet aggregation (Table 2).

Moreover, through many complex mechanisms insulin has anti-inflammatory, anti-apoptotic, and vasodilatory properties.[28]

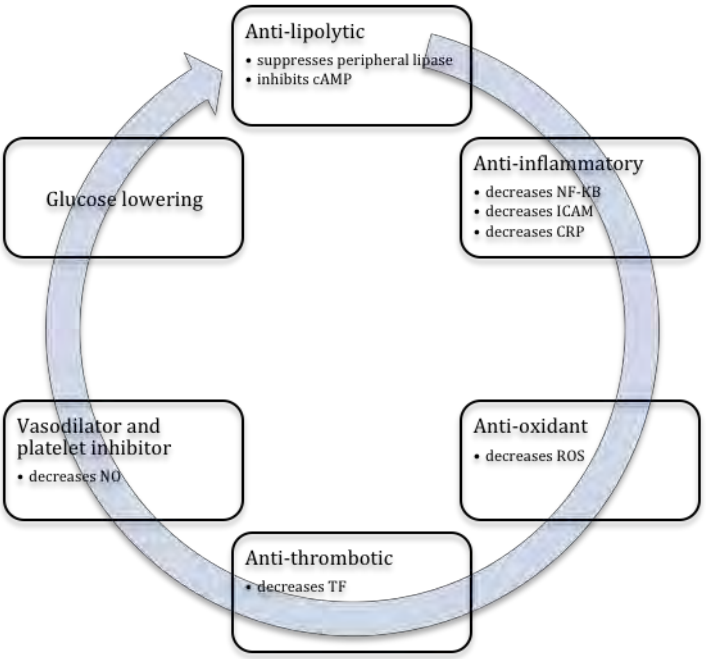


Figure 2. Mechanism of benefit for insulin in ischaemia

NF-KB indicates nuclear factor kappa beta; ICAM, intracellular adhesion molecules; CRP, C-reactive protein; ROS, reactive oxygen species; TF, tissue factor; NO, nitric oxide

Table 2. Mechanism of adverse effects of sustained hyperglycaemia in ischaemia[28]
Endothelial dysfunction
Platelet hyper-reactivity
Increased cytokine activation
Increased lipolysis & free fatty acid levels
Reduced glycolysis & glucose oxidation
Osmotic diuresis, potentially reduced cardiac output
Increased oxidative stress (increased myocardial apoptosis)
Impaired micro-circulatory function (no-reflow phenomenon)
Impaired insulin secretion & insulin stimulated glucose uptake

The role of potassium in GIK is to ensure myocardial cell membrane stability by preventing hypokalaemia, since the infusion would cause potassium to move intracellularly. The administration of exogenous potassium in safe doses therefore guards against this.[29,30]

A revival of the GIK concept has best been described in the recent review by Grossman et al. in which the cellular effects of GIK have been elaborated.[31] In a variety of animal and clinical models they supported the idea that GIK helps normalize intra-mitochondrial energy production by inhibiting the FFA-induced abnormalities. This correlates clinically to a reduction in infarct size, especially if given early.

Importance of this review

The traditional management of STEMI has ignored the role for metabolic modulation[5,6]. Reperfusion injury as a result of revascularisation confers an obvious risk, which may be attenuated with appropriate intervention. While there are many potential treatments (Table 1) in this regard, this review evaluates remote ischaemic preconditioning (RIPC) and glucose-insulin-potassium (GIK) as promising adjunctive therapies to revascularisation, which may prevent reperfusion injury, as suggested by both animal and human studies. The results from previous studies however have been unclear, as they have not administered RIPC or GIK early (before myocyte necrosis occurs).

The aims of this systematic review was therefore to summarize and quantitate (1) the risk of mortality in patients who underwent RIPC or GIK infusions and, (2) the risk of clinical outcomes (i.e. a reduction in infarct size, cardiac enzyme release or major adverse cardiac and cerebral events hospitalization) compared to patients who did not undergo RIPC or GIK.

The implications for practice would therefore be to make sense of available data from major trials and to provide recommendations for future research. It is also anticipated that the results from this review will inform better therapeutic practice, especially in the setting of low socio-economic countries like South Africa where cardiac catheterisation laboratories are not easily accessible.

METHOD

Participants: Human participants with coronary artery disease.

Intervention: Remote ischaemic preconditioning or glucose-insulin-potassium either alone or as adjunctive therapy to revascularisation.

Control: Placebo or standard therapy alone.

Outcome: Mortality, infarct size, cardiac enzyme release and major adverse cardiac and cerebral events.

Objectives

Primary objective: To determine whether participants receiving RIPC or GIK for coronary artery disease, and in particular STEMI, experience a reduction in mortality when compared to those patients not receiving them.

Secondary objectives:

1. To determine whether participants receiving RIPC or GIK experience a reduction in infarct size, cardiac enzyme release or major adverse cardiac and cerebral events (MACCE) when compared to those patients not receiving them.
2. To identify adverse effects associated with RIPC or GIK therapy..
3. To identify gaps in knowledge and where new trials are needed regarding the administration of RIPC or GIK.

Inclusion criteria:

We included all studies that met the following criteria:

- Human participants with coronary artery disease
- Intervention with RIPC or GIK either alone or in combination with revascularisation
- Studies that compared RIPC or GIK to control groups that did not receive them

- Outcome measured by mortality, reduction in infarct size, cardiac enzyme release or MACCE

Exclusion criteria:

We excluded studies that did not assess RIPC or GIK as part of therapy for coronary artery disease. In addition, general discussion papers not presenting data were excluded.

Search Strategy (Figure 3)

Academic research, local and international studies were targeted. Language restrictions included studies published in English. Study identification included both manual and electronic searching strategies. Electronic searches involved the electronic databases Cochrane and PubMed. The initial selection criteria were broad to ensure that as many studies as possible were assessed in terms of their relevance to the review. Any articles that were obviously unsuitable were excluded in the early stages of the search (for example, on the basis of abstracts and titles presented in electronic catalogues), whilst the decision to exclude or include other articles was made once the article was been ordered and read. The number of articles included and excluded at the various stages was noted and shortlisted based on the quality of their content in association with the inclusion criteria. The reference lists of articles identified by this strategy were also searched and we selected those that were judged relevant. Several review articles were included because they provide comprehensive overviews that are beyond the scope of this review.

Search Terms for Electronic Databases.

MeSH terms

The basic terms that were used when devising search strategies for electronic databases included “ischaemic preconditioning” or “ischemic preconditioning” and “glucose-insulin-potassium” AND “myocardial”.

A ‘search diary’ was maintained detailing the names of the databases searched, the keywords used and the search results. Titles and abstracts of studies considered for retrieval were recorded on a database, along with details of where the reference has been found. Inclusion/exclusion decisions were recorded on that database. Retrieved studies were filed according to inclusion/exclusion decisions.

Data collection, storage and analysis

Data was stored on an electronic database and reviewed based on the inclusion and exclusion criteria mentioned above.

All relevant material identified from the above search were analysed. After reading the titles and abstracts of the identified articles, we acquired the full text articles deemed to meet the inclusion criteria. These articles were independently inspected to verify that they met the pre-specified inclusion criteria.

Data was then extracted using a standardised data extraction form (Appendix 1). Any discrepancies were resolved through discussion of the original articles with the supervisors.

The following characteristics were extracted from each included study:

- Administrative details: trial identification number; title; author(s); published or unpublished; year of publication; number of studies included in paper; year in which the study was conducted; and details of other relevant papers cited

- Verification assessment: assessment to ensure that the study met the inclusion criteria for the systematic review, details of study

- Study design; duration and completeness of follow-up; country and location of study; informed consent; and ethics approval

- Risk of bias assessment: adequate sequence generation, allocation concealment, free of selective reporting, free of other bias, blinding

- Details of participants: setting; number; relevant baseline characteristics

- Details of intervention: dosage; duration; and mode of administration

- Details of control: placebo; and completeness of treatment

- Details of outcomes: mortality; morbidity and adverse effects of therapy

Quality assessment

Regular meetings were conducted with the supervisor Prof. Lionel H Opie at the Hatter Cardiovascular Research Institute where progress was monitored and critique obtained. Additional input was received from Dr. Mark Engel at the University of Cape Town.

Limitations of study

Studies have been selected in English only. The available studies on RIPC and GIK are fairly low powered. There is also no evidence on the role of RIPC as an adjunct to thrombolysis

Funding

The study was self-funded.

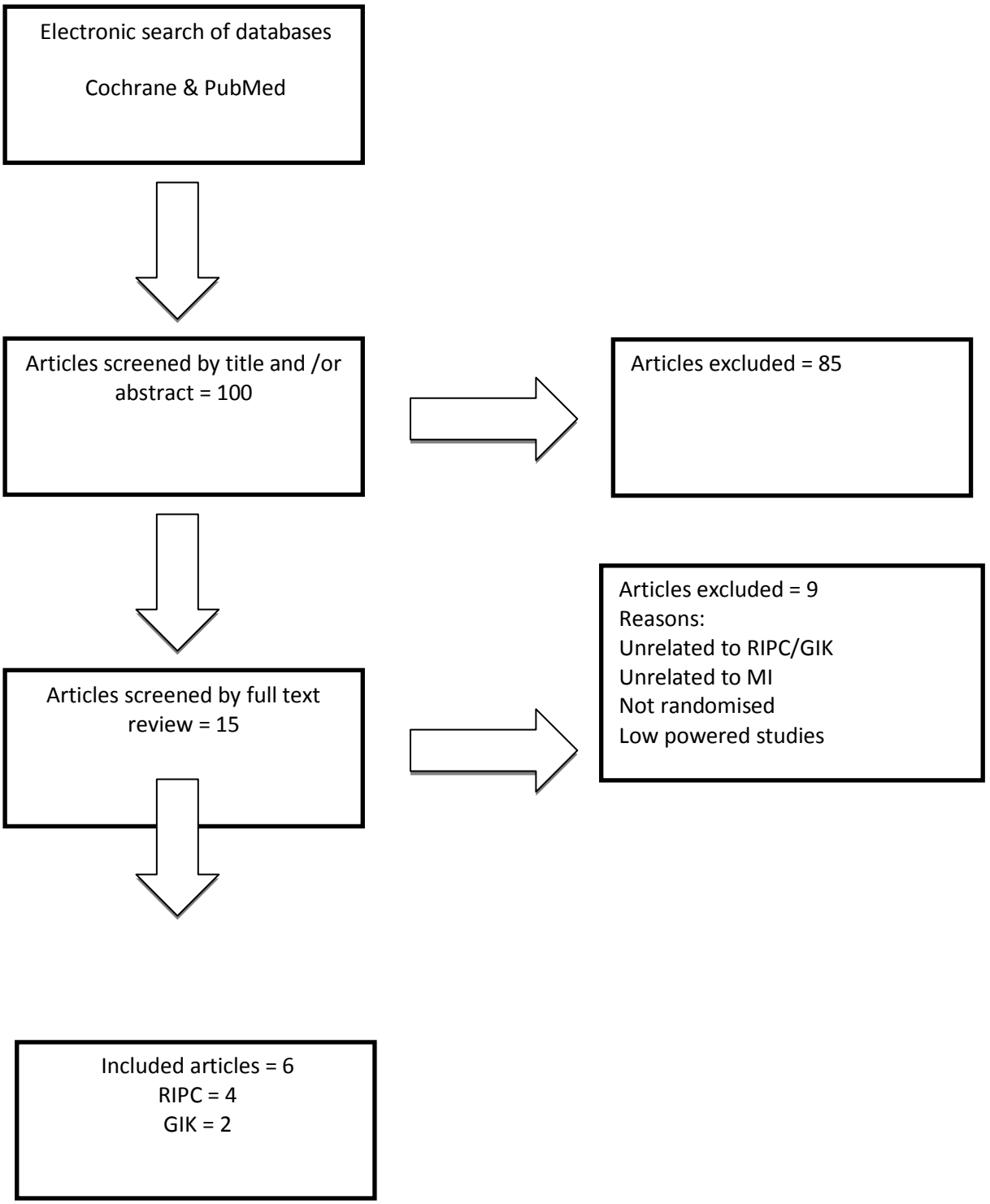
Ethics

There is no particular ethics breach associated with the project and ethics approval is not necessary for the purposes of a systematic review.

Declaration of interest

None.

Figure 3. Search strategy flow chart



RESULTS

GENERAL DESCRIPTION OF THE STUDIES FOR RIPC AND GIK

The search strategy identified 100 articles from 2 databases. Following review of the titles, 85 articles were excluded, leaving 15 studies for full-text review. Reasons for exclusion were studies that were unrelated to RIPC/GIK, unrelated to CAD, not randomised and low powered. Reasons for exclusion are shown in Table 5 (Appendix 2). Six articles were included in the final subset. Studies were located in America, Europe and the United Kingdom with sample sizes ranging between 45 and 20201 participants. Interventions included RIPC and GIK either alone or as adjunctive therapy to patients with CAD. Studies evaluated for the purpose of the systematic review were exclusively human studies (Figure 3) although a brief description of laboratory based animal studies are reported on to highlight the evolution of these therapies from the laboratory to clinical practice. The characteristics for inclusion were studies that were adequately powered, ideally placebo controlled, single or multi-centred and randomized (appendix 2).

RIPC in Animal Studies

Murray et al. first postulated the concept of ischaemic preconditioning in 1986 when they reported that episodes of sub-lethal regional ischaemia separated by periods of reperfusion for 40 minutes in the canine myocardium delayed the development of myocardial infarction.[32] It was proposed that the potential for cardio-protective benefit was attributable to reduced ATP depletion by decreasing ATP demand during periods of ischaemia as well as by reducing the accumulation of toxic metabolites. They asserted that slowing the rate of myocardial necrosis could thereby extend the window period for salvage by thrombolysis or angioplasty.

Opie subsequently coined the term “reperfusion injury” in 1989 and elaborated on its effect in myocardial function.[11] He explained that the two most important hypotheses in reperfusion injury included calcium overload, which interferes with mitochondrial oxygenation and ATP production, and free radical damage – a process that is accelerated during reperfusion. The consequences of this may be the basis for reperfusion arrhythmias, vascular damage and myocardial stunning.[33,34,35,36,37] This concept was tested for remote or distant areas of myocardium the 1990s by Pryzklenk who showed that the final infarct size in the hearts of dogs was reduced up to 35% by inducing brief periods of ischaemia in the circumflex artery following left anterior descending artery occlusion.[38] It was considered plausible that a systemic factor was responsible for mediating the preconditioning response. Amidst the growing interest elicited, subsequent human studies attempted to corroborate the cardio-protective effect found in these pre-clinical animal studies.

RIPC in Coronary Artery Bypass Grafting (CABG)

Hausenloy et al demonstrated in a small study of 57 patients that the total troponin T released 72 h after surgery was reduced from 36.12 µg/L (26.08) in control group to 20.58 µg/L (9.58) in the group treated with RIPC. The mean difference of 15.55 correlated with a 43% reduction in troponin T release (95% CI 4.88-26; p=0.005).[39] RIPC consisted of three 5-min cycles of right upper limb ischaemia, induced by an automated cuff -inflator placed on the upper arm and inflated to 200 mmHg, with an intervening 5 min of reperfusion during which the cuff was deflated whereas the control group had only a deflated cuff placed around the arm.

Similar results were obtained with Venugopal et al in 2009 in a small but positive study of 45 patients receiving coronary artery bypass with cold blood cardioplegia.[40] RIPC was administered in the same manner. The total troponin T released 72 h after surgery, was reduced from a mean of 31.53 (24.04) **m**g/L in controls to 18.16 (6.67) **m**g/L with RIPC (mean difference 13.37 mg/lL , 95% CI 2.41 to 24.33 mg/L, p=0.019) which translates to a 42% reduction in troponin post-operatively.

The ERICCA trial is a multi-centre, randomized, double-blinded, placebo-controlled clinical trial that is currently underway, which will recruit 1610 high-risk patients undergoing CABG ± valve surgery with or without RIPC.[41] The primary combined endpoint will be cardiovascular death, non-fatal myocardial infarction, coronary revascularization and stroke at 1 year. The findings, if positive, will have the potential to demonstrate that RIPC is an effective and safe intervention in high-risk patients undergoing CABG ± valve surgery.

RIPC in Percutaneous Coronary Intervention (PCI)

The most landmark study of RIPC as a complement to angioplasty was conducted by Botker in Denmark.[42] 333 randomised patients with first onset STEMI were enrolled, of which half received RIPC. In the RIPC group the primary endpoint of myocardial salvage at 30 days following PCI was assessed using myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment. The RIPC group showed a median salvage index of 0.75 vs. 0.57 in the control group without any associated increased risk (95% CI 0.01-0.22; p=0·0333).

RIPC has also been studied in elective PCI. The CRISP trial investigated 242 randomly assigned patients with undetectable pre-procedural Troponin I (TnI) undergoing elective PCI.[43] Subjects were randomized to receive remote IPC or to the control group before arrival in the catheter laboratory. For its primary end-point, the median TnI at 24 hours after PCI was lower in the RIPC compared with the control group (0.06 versus 0.16 ng/mL; p=0.04). Subjects who received remote IPC experienced less chest discomfort and ECG ST-segment deviation than control subjects. At 6 months, the major adverse cardiac and cerebral event (MACCE) rate was lower in the RIPC group (4 versus 13 events; 95% CI 0.12-0.82; p=0.018). Furthermore this benefit was sustained at 6 year follow up in 192 of the original 242 patients at 6 year follow up when MACCE remained lower in the RIPC group (23 versus 36 events; CI 95% 0.35-0.97; p=0.039; ARR=0.13; NNT=8).[44]

RIPC in Thrombolysis

The role of RIPC as an adjunct to thrombolysis has never been adequately studied, and to date there are no published trials in this regard. Ironically, this is most pertinent to the South African setting where revascularisation is mainly given in the form of thrombolysis rather than PCI. It is an urgent calling, and an opportunity, for local trials to investigate the matter further.

Table 3. RIPC as an adjunct to CABG, PCI & Thrombolysis

STUDY	PARTICPANTS		INTERVENTION	CONTROL	OUTCOME		
CABG							
Hausenloy[39]	n=57 undergoing elective CABG		3 five minute upper limb ischaemia with BP cuff inflated to 200mmHg	Deflated cuff placed around the arm	Trop T at 72 hours		
	Interv.	27			Interv	20.58	
	Control	30			Control	36.12	
Venugopal[40]	n=45 undergoing elective CABG		3 five minute upper limb ischaemia with BP cuff inflated to 200mmHg	Deflated cuff placed around the arm	Trop T at 72 hours		
	Interv.	23			Interv.	18.16	
	Control	22			Control	31.53	
PCI							
Botker[42]	n=333 with STEMI		4 five minute upper limb ischaemia with BP cuff inflated to 200mmHg	Standard PCI therapy only	Myocardial salvage index		
	Interv.	167			Interv.	0.75	
	Control	166			Control	0.57	
Hoole[43,44]	n=201 undergoing elective PCI (6mo follow up)		3 five minute upper limb ischaemia with BP cuff inflated to 200mmHg	Deflated cuff placed around the arm		Trop I at 24 hours	MACCE
	Interv.	104			Interv.	0.06	4
	Control	97			Control	0.16	13
THROMBOLYSIS							
No study currently							

RESULTS OF STUDIES WITH GIK

As will be discussed, over the past two decades there have been numerous studies and meta-analyses in the field of GIK as a cardio-protective therapy in acute myocardial infarction but their results have been extremely variable.

GIK in Animal Studies

Preclinical trials in animal models in the early 1970s mainly showed benefit of GIK in limiting myocardial necrosis.[45] Furthermore the benefits of GIK were shown in a primate model within one hour of coronary ligation.[46] GIK reduced the amount of circulating FFAs by 50% and final infarct size by 15%. The study emphasized the importance of early GIK administration during which period the opportunity for metabolic manipulation is greatest. Unfortunately, later clinical trials greatly overlooked the need for early therapy by GIK.[47]

GIK in Clinical Studies

In 1997 a meta-analysis by Fath-Ordoubadi et al noted a 28 % reduction in mortality when GIK was administered to patients with ACS. Although the study was performed before the reperfusion era it made important inferences regarding GIK and led the authors to conclude that GIK had an important role in improving mortality after ACS.[48]

The CREATE-ECLA trial, the largest of these studies, investigated the effects of GIK in 20201 patients with STEMI.[47] At 30 days, 976 control patients and 1004 GIK infusion patients died (HR 1.03; CI 95%; p=0.45). Furthermore, a neutral effect was demonstrated on cardiac arrest, cardiogenic shock and cardiac failure in those receiving GIK. The CREATE-ECLA trial however, was not double blinded nor placebo controlled. Flaws in its design also included a delay to GIK therapy (median time from symptom onset to treatment was approximately 5.7 hours) and non-uniformity in additional pharmacological therapy, such as statins and supplemental insulin. Moreover, these results were not well documented. Due to a disappointing outcome from the CREATE-ECLA trial,

the OASIS 6 study was prematurely terminated.

A meta-analysis by Kloner in 2008 studied 18 trials using both high and low dose GIK. He demonstrated that GIK led to an overall 18% reduction in mortality at 30 days.[48] Furthermore, this included studies on GIK performed at various times of onset after clinically diagnosed acute myocardial infarction. Although this is supportive of the GIK concept it does not directly give information as to the possible benefits of very early GIK therapy. It was recommended that future studies address the pitfalls of previous studies leaving the hypothesis that early GIK would reduce 30 day and 1 year mortality.

The recent 2013 review by Grossman et al. assessed the mechanisms whereby early GIK was given to a variety of animal models with coronary ligation or induced ischaemia, or to patients with early AMI in which GIK was demonstrated to be protective.[31] It was suggested that much of the clinical controversy relating to GIK was due its late application. The major benefit of GIK to act as a metabolic modulator they proposed, is when it is started within the first hours of symptom onset. In practical terms, this would best be initiated in the ambulance.

GIK in The Ambulance

Accordingly, the IMMEDIATE trial was launched to administer GIK in the ambulance.[50] This randomised, double blinded placebo controlled trial enrolled 871 patients with all acute coronary syndromes across 13 US cities. In it, paramedics in the field ensured the early start-up of the administration of GIK during the very first hours of ACS and continued the infusion for 12 hours thereafter. The first aim of lowering the circulating FFA levels was achieved in that at 2 hours after the start up in the ambulance the mean FFA values in the placebo group were 781 mmol/L versus 480 mmol/L in the GIK group (95% CI 269-465; $p<0.0001$). The subset of patients with STEMI derived significant benefit in that cardiac arrest and in-hospital mortality occurred in 6.1% with GIK vs. 14.4% with placebo (95% CI 0.18-0.82; $p=0.01$), although the primary end-point of progression to MI in those with unstable angina was not reduced, and 30 day mortality was the same across all forms of ACS.

Furthermore there was no increase in heart failure with GIK. LV infarct size was ameliorated from 12% with placebo to 3% with GIK (p=0.05). It should nonetheless be noted that the primary end point was not achieved because the initial NIH-approved study design was aimed at 15 450 patients to reach statistical significance but due to funding constraints only 871 patients were recruited thereby considerably lessening its statistical impact. Subsequently, Selker et al. recently published one-year outcomes after the IMMEDIATE trial, which demonstrated that for patients with STEMI, outcomes were significantly improved. HRs for 1 year mortality and the 3 composites of mortality, cardiac arrest, or heart failure hospitalization within 1 year were, respectively, 0.65 (95% CI 0.33 to 1.27, p = 0.21), 0.52 (95% CI 0.30 to 0.92, p = 0.03), 0.63 (95% CI 0.35 to 1.16, p = 0.14), and 0.51 (95% CI 0.30 to 0.87, p = 0.01).

Table 4. GIK as adjunctive therapy for Acute Coronary Syndromes

STUDY	PARTICIPANTS		INTERVENTION	CONTROL	OUTCOME					
Late administration of GIK										
CREATE-ECLA[47]	n=2021 with STEMI		GIK - 25% glucose, 50 U/L of regular insulin, and 80 mEq/L of KCL at 1.5 mL/kg/hr for 24 hours	Standard treatment alone (no placebo)		Mortality	Cardiac arrest	Cardioge-nic shock	Reinfarct-ion	Heart Failure
	Interv.	10091			Interv.	1004	139	667	236	1721
	Control	10110			Control	976	151	640	246	1711
Early administration of GIK										
IMMEDIATE[50]	n=842 with ACS n=357 with STEMI		GIK - 30% glucose, 50 U/L of regular insulin, and 80 mEq of KCl/L at 1.5 mL/kg/hr for 12 hours	5% glucose solution		ACS		STEMI subset		
						Mortality	Progress-ion to MI	In hospital mortality	Composite of cardiac arrest & mortality	
	Interv.	411			Interv.	18	200	6	10	
	Control	460			Control	28	242	14	28	

DISCUSSION

As an adjunct to CABG, the studies by Hausenloy and Venugopal showed a 43 & 42% reduction in cardiac enzyme release respectively.[39,40] Numerous studies have suggested that the release of cardiac enzymes post operatively is associated with myocardial injury and consequently greater morbidity and mortality (up to 4.9 fold increase in risk).[51,52,53] RIPC is therefore potentially cardioprotective in patients undergoing CABG.

When administered to patients undergoing emergency PCI the landmark Botker study showed an improvement in myocardial salvage.[42] Since a reduction in infarct size is a major determinant of prognosis, the study concluded that RIPC is a simple, low cost, effective therapy with a favourable safety profile in STEMI. [54] The CRISP study also corroborated the cardioprotective effect of RIPC as an adjunct to elective PCI and called on for larger scaled multi centred randomised controlled trials to be performed.[43,44]

RIPC has thereby demonstrated consistent and positive benefits in both proof of principle experimental & clinical trials targeting biochemical pathways that had not been considered previously. The extraordinary simplicity associated with RIPC implies that even a paramedic, a junior medical officer or nurse in an emergency room can perform the BP cuff inflations. Thus it has become routine practice in Denmark to perform RIPC in patients with ACS in the ambulance en route to a health care facility.

Trials investigating GIK demonstrated conflicting and mostly negative results but were confounded by many variables such as the fixed dose regimens administered, failure to consider the volume or metabolic status of the patient and, importantly, a lack of emphasis on the relationship between the time of delivery of GIK and reperfusion.[47,55,56,57] The only study to address this adequately has been the IMMEDIATE trial.[50] It demonstrated a reduction in in-hospital mortality, cardiac arrest and LV infarct size in the STEMI subset of patients. The study also emphasized the importance of start up time of GIK therapy as suggested by Grossman et al in their 2014 review of GIK.[31] The IMMEDIATE trial is also the only metabolic trial with outcome data initiated in the ambulance and the only trial in

which GIK infusion was started within 1 hour of symptom onset thereby highlighting the potential benefit of GIK as an early metabolic modulator in STEMI.

CONCLUSION

Recommendations for research

As indicated, higher-powered studies are needed to firmly establish the role of RIPC and GIK in the management of CAD. RIPC in the setting of thrombolysis has also not been studied previously and is an area for further research. Furthermore, there should be large scale, double blinded, multi centred studies that compare RIPC with GIK and with the combination. In view of the different mechanisms of RIPC and GIK the hypothesis would be a greater therapeutic benefit for the combination.

Recommendations for practice

The incidence of CAD is increasing and traditional practice largely ignored the impact of ischemic reperfusion injury. Attention however is slowly shifting towards viewing myocardial infarction as not just a mechanical disease but also a metabolic one in which both ischaemia & ischaemic reperfusion contribute to cardiomyocyte injury. South Africa, and other developing countries are in a challenging position to use all available positive and safe therapies that confer benefit given its limitations in accessibility to angiographic facilities. RIPC or GIK should therefore be considered as part of an armamentarium of adjunctive treatment strategies, to curb ischemic reperfusion injury and augment the benefit of revascularisation. More large scale, multi-centered randomised controlled trials are however needed to evaluate this further.

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APPENDIX 1

Data Extraction Sheet

Administrative details	
Study ID	
Trial Number	
Publication details	
Year of publication	
Number of studies in this paper	
Year in which study was conducted	
Other relevant papers cited	
Language published	
Number of citations	
Authors	

Study details	
Study verification	
Study design	
Type, duration and follow up	
Country of study	
Informed consent	
Ethics obtained	
Funding of studies	
Conflicts of interest	

Participant details	
Diagnosis	

Number of participants	
Baseline characteristics	

Interventions	
Dosage	
Time to administration of therapy	
Control	
Background treatment	

Risk of bias	
Adequate sequence generation	
Allocation concealment	
Free of selective reporting	
Free of other bias	
Blinding	

Primary outcome	
Mortality	
Immediate	
30 days	
1 year	
5 years	

Secondary outcomes	
Morbidity including major adverse cardiovascular events	
Adverse effects of therapy	
Cost of therapy	

APPENDIX 2

Characteristics of Included Studies: RIPC

Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial[20] Lancet 2007; 370: 575–79 Derek J Hausenloy, Peter K Mwamure, Vinod Venugopal	
Participants	Diagnosis = CAD
	Number = 57
	18-80, M 80%, diabetics 43%
Intervention	Three 5-min cycles of right upper arm ischaemia, which was induced by an automated cuff -inflator placed on the right upper arm and inflated to 200 mm Hg, with an intervening 5 min of reperfusion during which the cuff was deflated prior to CABG
Control	Did not receive RIPC
Outcome	The total troponin-T released 72 h after surgery was reduced from 36.12 µg/L (26.08) in control group to 20.58 µg/L (9.58) in the remote ischaemic preconditioning group. 95% CI; p=0.005
	There were no untoward results of the remote ischaemic preconditioning protocol.

Remote ischaemic preconditioning reduces myocardial injury in patients undergoing

cardiac surgery with cold-blood cardioplegia[24] *Heart* June 8 2009. DOI:10.1136 Venugopal V, Hausenloy DJ, Ludman A	
Participants	Diagnosis = CAD
	Number = 45
	Adults patients (18–80 years) undergoing elective CABG surgery with or without concomitant aortic valve surgery with cold-blood cardioplegia. Patients with diabetes, renal failure (serum creatinine **.**130 mmol/l), hepatic or pulmonary disease, unstable angina were excluded Patients and the cardiac surgeons were blinded to treatment allocation, although the investigators and anaesthetists were not blinded
Intervention	RIPC comprised three 5 min cycles of right forearm ischaemia, induced by inflating a blood pressure cuff on the upper arm to 200 mm Hg, with an intervening 5 min reperfusion.
Control	Did not receive RIPC
Outcome	RIPC reduced absolute serum troponin T release by 42.4% (mean (SD) AUC at 72 h: 31.53 (24.04) **m**g/ l.72 h in controls vs 18.16 (6.67) **m**g/l.72 h in RIPC; 95% CI 2.4 to 24.3; p=0.019).

Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent)[25] *Circulation*. 2009;119:820-827

Stephen P. Hoole, Patrick M Heck	
Participants	Diagnosis = CAD
	Number = 242
	Two hundred forty-two consecutive patients undergoing elective PCI with undetectable preprocedural cTnI were recruited. All patients 18 of age who were undergoing elective PCI and able to give informed consent were eligible for study.
Intervention	3 cycles of BP cuff inflation to 200-mm Hg pressure for 5 minutes, followed by 5 minutes of deflation followed by PCI
Control	Did not receive RIPC
Outcome	In those patients who received remote IPC before elective PCI, the MACCE rate at 6 months was lower (4 hospital admissions with an acute coronary syndrome versus 13 events in the control group. The median cTnI at 24 hours after PCI was lower in the remote IPC compared with the control group (0.06 versus 0.16 ng/mL; **P_** 0.040). After remote IPC, cTnI was **_** 0.04 ng/mL in 44 patients (42%) compared with 24 in the control group (24%; **P_** 0.01). Subjects who received remote IPC experienced less chest discomfort (**P_** 0.0006) and ECG ST-segment deviation (**P_** 0.005) than control subjects. At 6 months, the major adverse cardiac and cerebral event

	rate was lower in the remote IPC group (4 versus 13 events; **P_** 0.018). In those patients who received remote IPC before elective PCI, the MACCE rate at 6 months was lower (4 hospital admissions with an acute coronary syndrome versus 13 events in the control group

Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial[26] Lancet 2010; 375: 727–34 Hans Erik Bøtker, Rajesh Kharbanda, Michael R Schmidt	
Participants	Diagnosis = CAD
	Number = 333
	Age 62, Men 75-6%, HPT 24-38%, DM 9%, Smokers 56-7%
Intervention	PCI + RIPC (4 cycles alternating inflation & deflation of BP cuff to 200mmHg)
Control	Did not receive RIPC
Outcome	Myocardial salvage index in the remote conditioning group in the control group was 0·69 (SD 0·27) versus 0·57 (0·26) with mean difference of 0·12 (95% CI 0·01–0·21, p=0·0333); At 30 days, left ventricular ejection fraction was not signifi cantly different between the groups, and we recorded no differences in major adverse coronary events (in

	each group, three patients died, one had reinfarction, and three developed heart failure; p=1·0) or in NYHA class (p=0·75).

Characteristics of Included Studies: GIK

Effect of Glucose-Insulin-Potassium Infusion on Mortality in Patients With Acute ST-Segment Elevation Myocardial Infarction *JAMA*. 2005; 293:437– 446 Mehta SR, Yusuf S.	
Participants	Diagnosis = CAD
	Number = 20201
	Age 58, M 78%, DMT2 17.8%, HF 1.7%
Intervention	The study infusion was prepared locally and consisted of 25% glucose, 50U/L of regular insulin, and 80 mEq/L of potassium to be infused at a rate of 1.5 mL/kg per hour for 24 hours.
Control	Did not receive GIK but not placebo based
Outcome	At 30 days, a total of 976 control patients (9.7%) and 1004 GIK infusion patients (10.0%) died within 30 days of randomization. Cardiac arrest occurred in 151 control patients (1.5%) and in 139 GIK infusion patients (1.4%) (HR, 0.93; 95% CI, 0.74-1.17; **P**=.51). Cardiogenic shock developed in 640 control patients (6.3%) and 667 GIK infusion patients (6.6%) (HR, 1.05; 95% CI, 0.94-1.17; **P**=.38).

Out-of-Hospital Administration of Intravenous Glucose-Insulin-Potassium in Patients With Suspected Acute Coronary Syndromes *JAMA.* 2012; 307: 1925-33 Harry P. Selker, Joni R. Beshansky, Patricia R. Sheehan	
Participants	Diagnosis = CAD
	Number = 871
	Mean age 63, M 71%, Patients with clinically significant HF (more than basilar rales), renal failure requiring dialysis, or who were unable to give informed consent were excluded.
Intervention	The GIK solution was 30% glucose (300 g/L), 50 U/L of regular insulin, and 80 mEq of KCl/L administered intravenously using portable infusion pumps at 1.5 mL/kg/h (approximately 100 mL/h for a 70-kg patient)17 for 12 hours.
Control	Did not receive GIK
Outcome	For the major secondary end points, 30-day mortality was 4.4% with GIK vs 6.1% with placebo (hazard ratio [HR], 0.72; 95% CI, 0.40-1.29; **P**=.27); the composite end point of cardiac arrest or in-hospital mortality occurred in 4.4% with GIK vs 8.7% with placebo (OR, 0.48; 95% CI, 0.27- 0.85; **P**=.01). In STEMI subset Thirty-day mortality was 4.9% with GIK vs 7.7% with placebo the composite of cardiac arrest or inhospital mortality occurred in 6.1% with GIK vs 14.4% with

	placebo (OR, 0.39; 95% CI, 0.18-0.82; **P**=.01).

Characteristics of Excluded Studies: RIPC

Remote ischemic preconditioning in percutaneous coronary revascularization: a double-blind randomized controlled clinical trial *Asian Cardiovascular & Thoracic Annals 2012*; 20(5) 548–554 Ali Ghaemian1, S Mahmoud Nouraei1, Fatemeh Abdollahian	
Reason for exclusion	Lack of blinding and heterogeneity between RIPC and control groups. Sequence generation and allocation concealnment was unclear. It was also a low powered study.

Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2013 Nov 1;82(5):E647-53 Ahmed RM, Mohamed el-HA, Ashraf M, Maithili S, Nabil F, Rami R, Mohamed TI	
Reason for exclusion	Lack of blinding and heterogenity between RIPC and control groups. It was also a low powered study.

Myocardial remote ischemic preconditioning: from pathophysiology to clinical application. Rev Port Cardiol. 2013 Nov;32(11):893-904 Costa JF, Fontes-Carvalho R, Leite-Moreira AF.	
Reason for exclusion	Risk of bias due to unclear sequence generation and allocation concealnment was unclear.

Remote ischemic preconditioning reduces myocardial injury in patients undergoing

coronary stent implantation. Luo SJ, Zhou YJ, Shi DM, Ge HL, Wang JL, Liu RF. Can J Cardiol. 2013 Sep;29(9):1084-9.	
Reason for exclusion	Heterogeneity in renal function

Remote ischemic preconditioning reduces cardiac troponin I release in cardiac surgery: a meta-analysis. Yang L, Wang G, Du Y, Ji B, Zheng Z. J Cardiothorac Vasc Anesth. 2014 Jun;28(3):682-9.	
Reason for exclusion	Participants included paediatric patients undergoing cardiac surgery, valve procedures, and correction of congenital cardiac anomalies

Remote ischaemic preconditioning versus no remote ischaemic preconditioning for vascular and endovascular surgical procedures. Desai M, Gurusamy KS, Ghanbari H, Hamilton G, Seifalian AM. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD008472	
Reason for exclusion	Participants included patients undergoing open vascular or endovascular surgery which was not related to CAD

Effect of Remote Ischemic Preconditioning in the Elderly Patients With Coronary Artery Disease With Diabetes Mellitus Undergoing Elective Drug-Eluting Stent Implantation. Xu X, Zhou Y, Luo S, Zhang W, Zhao Y, Yu M, Ma Q, Gao F, Shen H, Zhang J. Angiology. 2013 Oct 24.	
Reason for exclusion	Limited patient population

Remote ischemic preconditioning immediately before percutaneous coronary intervention does not impact myocardial necrosis, inflammatory response, and circulating endothelial progenitor cell counts: a single center randomized sham controlled trial. Prasad A, Gössl M, Hoyt J, Lennon RJ, Polk L Catheter Cardiovasc Interv. 2013 May;81(6):930-6.	
Reason for exclusion	Primary and secondary objectives not met in this study

Effect of one-cycle remote ischemic preconditioning to reduce myocardial injury during percutaneous coronary intervention. Zografos TA, Katritsis GD, Tsiafoutis I, Bourboulis N, Katsivas A, Katritsis DG. Am J Cardiol. 2014 Jun 15;113(12):2013-7.	
Reason for exclusion	Suboptimal number of cycles for RIPC administered

Cardioprotective role of remote ischemic periconditioning in primary percutaneous coronary intervention: enhancement by opioid action. Vavetsi S , Pyrgakis V and Deftereos S JACC. Cardiovascular interventions, 2010, 3(1), 49	
Reason for exclusion	Opiods were not included in the study design for our review

Characteristics of Excluded Studies: GIK

Influence of different glucose -insulin -potassium regimes on glucose homeostasis and hormonal response in cardiac surgery patients . Boldt J , Knothe C , Zickmann B , Dünnes S , Dapper F and Hempelmann G Anesthesia and analgesia, 1993, 76(2), 233	
Reason for exclusion	Primary and secondary objectives not met

Influence of glucose -insulin -potassium on left ventricular function during coronary artery bypass grafting. Brodin LA , Dahlgren G , Ekeström S , Settergren G and Ohqvist G Scandinavian journal of thoracic and cardiovascular surgery, 1993, 27(1)	
Reason for exclusion	Primary and secondary objectives not met in this study

Myocardial protection by glucose-insulin-potassium in acute coronary syndrome patients undergoing urgent multivessel off-pump coronary artery bypass surgery. Shim JK, Yang SY, Yoo YC, Yoo KJ, Kwak YL. Br J Anaesth. 2013 Jan;110(1):47-53	
Reason for exclusion	Low powered study

Effect of perioperative glucose-insulin-potassium infusions on the prognosis in patients undergoing coronary artery bypass grafting: a meta-analysis. Liang YY, Zheng H, Chen CL, Guo H. Zhonghua Wai Ke Za Zhi. 2012 Nov;50(11):1021-6	
Reason for exclusion	Inconsistencies with infusions (some did not contain potassium)

Glucosa-Insulin-Potassium (GIK) solution used with diabetic patients provides better recovery after coronary bypass operations. Straus S, Gerc V, Kacila M, Faruk C. Med Arch. 2013;67(2):84-7.	
Reason for exclusion	Low powered study

TABLE 5

Summary of excluded studies for RIPC and GIK

Unrelated to RIPC/GIK
Unrelated to CAD
Not randomised
Low powered studies