Remote ischaemic preconditioning for coronary artery bypass grafting (Protocol)

Benstoem C, Stoppe C, Liakopoulos OJ, Meybohm P, Clayton TC, Yellon DM, Hausenloy DJ, Goetzenich A

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[Intervention Protocol]

Remote ischaemic preconditioning for coronary artery bypass grafting

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits and harms of remote ischaemic preconditioning in patients undergoing coronary artery bypass grafting, with or without valve surgery.

BACKGROUND

Cardiovascular disease (CVD) is the major contributor to the burden of disease and the number one cause of death worldwide. In 2008, 30% of all global deaths (17.3 million) were attributed to CVD (World Health Organization 2015). Of these deaths, an estimated 7.3 million were due to coronary artery disease (World Health Organization 2011).

Coronary artery disease (CAD) results from progressive blockage of the coronary arteries by atherothrombosis (Bojar 2011). Clinical syndromes result from an imbalance of oxygen supply and demand resulting in inadequate myocardial perfusion (ischaemia). CAD can be treated with medical therapy, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The patient's clinical presentation, the extent and nature of coronary disease, the degree of inducible ischaemia on stress testing and the status of ventricular function are taken into consideration when determining whether a patient is at increased risk of an adverse cardiac event and is therefore an appropriate candidate for an

interventional procedure (Patel 2009). An indication for CABG should be considered if PCI is not feasible or when the short- and long-term benefits of CABG are superior to those of PCI (Bojar 2011).

Despite substantial improvements in myocardial preservation strategies, cardiac surgery is still associated with severe complications. The incidence of complications will further increase in the future as cardiac surgery is increasingly being performed on an aging patient population with increased numbers of comorbid conditions and complex coronary lesions. Analyses of large patient databases indicate that major complications including death, myocardial infarction, cardiac arrest and failure, renal failure, stroke, gastrointestinal complications and respiratory failure occur in up to 16% of all patients during the initial hospital stay (Ghosh 2004).

Description of the condition

Worldwide, an estimated 800,000 to 1,000,000 CABG procedures are performed annually, with about 400,000 in the US alone (Centers for Disease Control and Prevention 2015). Most commonly, the procedure is performed through a median sternotomy with the use of cardiopulmonary bypass (CPB) and cardioplegic arrest. Revascularisation during CABG is obtained by creating new routes for the blood (bypasses) around narrowed or blocked coronary arteries. Autologous venous or arterial graft material is harvested from the patients' extremities and re-implanted in aorto-coronary position. In addition to the open surgical procedure under circulatory arrest, both minimally invasive and beating heart strategies exist.

Several approaches have been implemented to reduce the perioperative risk of myocardial ischaemia. Among the most commonly applied are hypothermia, cardioplegic solutions and the general limitation of procedure times. These strategies have led to a pronounced reduction in procedural mortality and morbidity (Estafanous 2001). Nevertheless, postoperative elevated creatine kinase or troponin levels indicate persisting myocardial damage due to intraoperative ischaemia reperfusion (I/R) injury. Methods of pre- and post conditioning have been proven to reduce I/R damage in vitro, however the translation into a clinically relevant protective strategy is still challenging.

Description of the intervention

Ischaemic preconditioning is an experimental method to increase the body's resistance to a projected reduced oxygen supply. In the heart, ischaemic preconditioning is an intrinsic process whereby repeated short episodes of ischaemia protect the myocardium against successive ischaemic insults.

Since the mid-1980s, the existence of preconditioning as a protective mechanism has been known from animal models (Murry 1986). A brief stimulus of sub-lethal ischaemia was able to induce at least two time windows in which the myocardium is protected from otherwise deleterious noxa. In recent decades, several alternative stimuli (e.g. opioids, volatile anaesthetics, noble gases) have been shown to induce the same effect. Amazingly, the effect can also be induced by a remotely applied temporary ischaemia. The term remote ischaemic preconditioning (RIPC) was first coined by Przylenk in 1993 (Przyklenk 1993). The remote ischaemic preconditioning intervention is performed by temporary inflation of a blood pressure cuff above the systolic arterial pressure on one chosen extremity. The blood flow from and to this extremity is blocked and local ischaemia occurs. Reperfusion washes released mediators from the isolated tissue into the circulation.

Within the past decade, remote ischaemic preconditioning has been rapidly translated from experimental studies to promising proof-of-principle clinical trials. Various studies have demonstrated that RIPC reduces myocardial injury in various surgical settings (Ali 2007; Cheung 2006; Hausenloy 2007; Hausenloy 2010; Hausenloy 2012; Heusch 2012; Thielmann 2010). In contrast, other reports have not confirmed the positive effects of RIPC (Karuppasamy 2011; Young 2012). The underlying reasons might be the RIPC protocol itself or the use of volatile anaesthetics in several of these studies, which in itself is known to protect the heart against ischaemia/reperfusion injury (Karuppasamy 2011; Kottenberg 2012).

Currently, the adverse events associated with RIPC are not known. The repeated pumping up of the blood pressure cuff is considered to be safe, and since the intervention occurs after the induction of anaesthesia, additional pain or feelings of stress through the actual intervention are unlikely. The potential risk of thrombosis, plaque rupture or embolisation in patients with pre-existing atherosclerosis in the upper extremities is also regarded as low.

How the intervention might work

In remote ischaemic preconditioning, temporal ischaemia of a distant compartment positively affects the human heart. The humoral factors involved are unclear, but it is largely agreed upon that the effect is mediated via the blood stream. Suspected mediators are nitrites (Corti 2014; Rassaf 2014), microRNA (Li 2014; Slagsvold 2014), and other chemokines. Within the myocardium, the effect is supposedly mediated via the reperfusion injury salvage kinase (RISK) and survivor activating factor enhancement (SAFE) pathways (Hausenloy 2011), and preserves mitochondrial function (Slagsvold 2014) and myocardial performance (Illes 1998; Li 1999; Lu 1997) in ischaemia/reperfusion.

Why it is important to do this review

Several randomised trials comparing RIPC versus no RIPC in patients undergoing CABG have been conducted, but the results have varied and most trials were too underpowered to reach a con-

clusion on clinically relevant outcome measures. Following the conduct of several small trials, two major trials on remote ischaemic preconditioning are currently completing recruiting and will provide data on 3012 patients undergoing CABG/cardiac surgery (Hausenloy 2012a; Meybohm 2012). Final consensus is needed on the effectiveness of RIPC for cardiac patients scheduled for CABG.

OBJECTIVES

To assess the benefits and harms of remote ischaemic preconditioning in patients undergoing coronary artery bypass grafting, with or without valve surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported in full text, those published as an abstract only and unpublished data.

Types of participants

We will include adult patients (≥ 18 years) with a diagnosis of acute coronary heart disease scheduled for CABG (with or without valve surgery).

Types of interventions

We will include trials comparing remote ischaemic preconditioning before CABG (with or without valve surgery) with no remote ischaemic preconditioning before CABG (with or without valve surgery).

Types of outcome measures

As no core outcome set for clinical studies investigating CABG is available, the list of outcomes chosen is based on outcome measures from possible matching studies.

Primary outcomes

1. Cardiac troponin T (cTnT) after CABG (ng/ml or µg/l)
2. Cardiac troponin I (cTnI) after CABG (ng/ml or µg/l)
3. Composite endpoint; if we are able to assess a composite endpoint e.g. major adverse cardiocerebral events (MACCE) as primary outcome, we will do so. However, due to inconsistency in defining clinical outcomes/composite endpoints in cardiac trials (Benstoem 2015) we are not able to define e.g. MACCE at this stage, but we will perform meta-analysis only if appropriate.

Secondary outcomes

1. All-cause mortality after 30 days
2. Major adverse cardiac events after 30 days
3. Stroke after 30 days
4. Acute renal failure after 30 days
5. Length of stay on the intensive care unit (hours)
6. Any complications and adverse effects related to ischaemic preconditioning, as reported by trial authors
7. Any patient-centred/salutogenic focused outcome, as reported in included studies

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE (Ovid);
- Web of Science (Thomson Reuters).

We will use the search strategy developed by the Cochrane Heart Group. We will adapt the preliminary search strategy for MEDLINE (Ovid) (Appendix 1) for use in the other databases. We will apply the Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/) for possible matching studies.

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will contact authors for missing data. We will contact the principal investigators of identified studies to ascertain if they are aware of any other relevant published or unpublished matching clinical studies.

Data collection and analysis

Selection of studies

We will import citations from each database into the reference management software Endnote, where we will remove duplicates. Two authors (CB, CS) will independently screen the titles and abstracts of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, we will ask a third author to arbitrate (AG).

We will retrieve the full-text study reports/publication and two authors (CB, AG) will independently screen the full text and identify studies for inclusion. We will identify and record reasons for the exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (CS). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a purposely pre-developed data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (CB, CS) will extract the following study characteristics from the included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of condition (e.g. number of affected vessels, left ventricular ejection fraction), inclusion and exclusion criteria, reported differences between intervention and comparison groups.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two authors (CB, AG) will independently extract outcome data from the included studies. We will resolve disagreements by consensus or by involving a third author (CS). One author (CB) will transfer data into The Cochrane Collaboration's statistical software Review Manager (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second author (AG) will check the study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two authors (CB, AG) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (CS). We will summarise the results of the 'Risk of bias' assessment in both a 'Risk of bias' graph and a 'Risk of bias' summary. Seven risk of bias domains have been identified and we outline below how we will assess the risk in relation to each of these domains.

Random sequence generation (checking for possible selection bias)

For each included study, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. The method will be assessed as follows:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk (insufficient information to permit judgement).

Blinding of participants and personnel (checking for possible performance bias)

We will describe whether participants and personnel were blind to the allocation to the intervention or control groups in our 'Risk of bias' assessment. We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

Blinding of outcome assessment (checking for possible detection bias)

For each included study, we will describe the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will consider studies to be at low risk of bias if they were blinded or if we judged that the lack of blinding could not have affected the results. We will assess the method as follows:

- low risk (no blinding of outcome assessment but the authors judged that the outcome was not likely to be influenced by this);
- high risk (no blinding of outcome assessment and the outcome measurement was likely to have been influenced by this);
- unclear risk (insufficient information to permit judgement; the study did not address this).

Allocation concealment (checking for possible selection bias)

For each included study, we will describe the method used to conceal the allocation sequence and determine whether the intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We will assess the method as follows:

- low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk (insufficient information to permit judgement).

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

For each included study and for each outcome or class of outcomes, we will describe the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion where reported, and whether missing data are balanced across groups or are related to outcomes. We will assess the method as follows:

- low risk (20% or less missing data);
- high risk (more than 20% missing data);
- unclear risk (insufficient reporting to permit judgement; the study did not address this).

Selective reporting (checking for reporting bias)

We will investigate the possibility of selective outcome reporting bias by identifying the outcomes in the study protocol (if available) and in the methods section of the publication, and by cross-checking to see if these outcomes are reported in the results section of the trial publication(s). We will assess the method as follows:

- low risk (where it was clear that all of the study's prespecified outcomes as identified in the study protocol (where available) and in the methods section were reported on; that all expected outcomes of interest to the review were reported on);
- high risk (where it was clear that not all of the study's prespecified outcomes as identified in the study protocol (where available) and in the methods section were reported on; failure to include a key outcome that would have been expected to have been included);
- unclear risk (insufficient information to permit judgement).

Other bias (checking for other biases)

For each included study, we will describe any important concerns we had about other possible sources of bias, for example sources of research funding. We will assess whether each study was free of other problems that could put it at risk of bias as follows:

- low risk (study appeared to be free of bias);
- high risk (had at least one important risk of bias, for example related to study design);
- unclear risk (insufficient information to permit judgement).

We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will interpret the results of the systematic review and meta-analyses in light of the findings with respect to risk of bias. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CI). For continuous data, we will use the mean difference with 95% CI for outcomes measured in the same way between trials. We will use the standardised mean difference (SMD) with 95% CI to combine data where the same outcome was measured but using different scales.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

As we will only include RCTs with a parallel design, therefore we do not expect unit of analysis issues to occur.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity

analysis**.** We will carry out analyses on an intention-to-treat basis for all outcomes, as far as possible.

Assessment of heterogeneity

Where we pool data using meta-analysis, we will assess the presence heterogeneity by visual inspection of forest plots and by examining the Chi² test for heterogeneity. We will also assess statistical heterogeneity in each meta-analysis using the Tau² (tau-squared), I² and X² (Chi²) statistics. We will regard heterogeneity as substantial if:

- the I² value is high (exceeding 30%); and either
- there is inconsistency between trials in the direction or magnitude of effects (judged visually), or there is a low P value (< 0.10) in the Chi² test for heterogeneity; or
- the estimate of between-study heterogeneity (Tau²) is above zero.

If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes by assessing funnel plot asymmetry visually and by using formal tests for funnel plot asymmetry (Egger 1997; Harbord 2006). If asymmetry is detected in any of these tests, or is suggested by a visual assessment, we will perform exploratory analyses to investigate it. If there are fewer than 10 studies included in this systematic review, we will assess reporting bias qualitatively based on the characteristics of the included studies.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

Given the clinical heterogeneity in the modus operandi of RIPC and the heart surgery performed (CABG with or without valve surgery) we will use random-effects meta-analysis to produce an overall summary of average treatment effect across trials. We will treat the random-effects summary as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials. We will present results as the average treatment effect with its 95% confidence interval, and the estimates of T² and I².

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful and, if it is, use random-effects analysis to produce it. We plan to carry out the following subgroup analyses.

- Differences in the number of RIPC cycles or their length.
- Differences in the localisation of RIPC (upper or lower limb).
- Differences in surgical techniques (off-pump versus on-pump CABG).
- Differences in concomitant or no concomitant cardiovascular procedure to CABG (with or without valve surgery). We will distinguish between isolated or combined valve procedures (e.g. aortic valve and/or mitral valve repair).

Where subgroup analyses are performed we will restrict them to the primary outcomes. We will use the formal test for subgroup interactions in Review Manager (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² test and P value, and the I² value of the interaction test.

Sensitivity analysis

We will perform sensitivity analysis by limiting analyses to studies at low risk of bias. This will be done by excluding studies judged at high or unclear risk of bias for sequence generation, allocation concealment and incomplete outcome data. We will give the criteria for these judgements in the 'Assessment of risk of bias in included studies' section.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary search strategy - MEDLINE (Ovid)

1 exp Ischemic Preconditioning/
2 (isch?em* adj2 (precondit* or pre-condit* or "pre condit*")).tw.
3 IPC.tw.
4 or/1-3
5 exp Coronary Disease/
6 coronary heart disease.tw.
7 exp Coronary Artery Bypass/
8 aortocoronary bypass.tw.
9 cabg.tw.
10 (coronary adj5 bypass).tw.
11 or/5-10
12 4 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 exp animals/ not humans.sh.
23 21 not 22
24 12 and 23

WHAT'S NEW

Date	Event	Description
19 November 2015	Amended	Re-published protocol with Gold Open Access
19 November 2015	New citation required and minor changes	no change

CONTRIBUTIONS OF AUTHORS

CB is the primary contact author for this protocol. CB co-ordinated the protocol.

CB, CS and AG led the conception, design and drafting of this protocol.

OJL, PM, DH, DMY and TTC contributed methodological expertise to the design and drafting of the protocol.

All authors contributed important content to the drafting of this protocol and approved the final protocol.

DECLARATIONS OF INTEREST

CS and PM are investigators of the RIPHeart Study (unpublished at the time this protocol was published), which investigates the effects of remote ischaemic preconditioning in cardiac surgery patients.

DJH and DMY are investigators of the ERICCA trial (unpublished at the time this protocol was published), which investigates the effects of remote ischaemic preconditioning in patients undergoing CABG.

TCC received funding support for the ERICCA trial in role as co-PI

If during this review we are able to assess data from the RIPHeart or ERICCA study, we will disclose this in our review and there will be an independent assessment of eligibility and risk of bias by CB and AG.

CB, AG and OJL have no conflict of interest.