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Cardioprotection in CABG and AVR patients with RIPC

Submission date
25/03/2013

Recruitment status
No longer recruiting

Registration date
25/03/2013

Overall study status
Completed

Last Edited
17/12/2018

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
During conventional open-heart surgery, the blood supply is diverted from the heart and lungs, to allow the operation to be carried out in a still and blood-free environment. The heart is carefully protected in order to prevent damage. However, a small degree of damage can occur due to the reduced blood flow. To minimise this, techniques have been used to protect the heart from injury and one such technique is the process of remote ischaemic preconditioning (RIPC). This is the simple application of several cycles of inflating and deflating a blood pressure cuff to the arm before heart surgery. Although some trials have suggested that RIPC protects the heart of child and adult patients undergoing open heart surgery using cardiac arrest (CA), other trials have reported that RIPC is ineffective. Reasons for the differing results may include the use of different surgical and anaesthetic techniques. Understanding the nature of any changes triggered in the heart by RIPC before and after cardiac arrest is a key step in optimising RIPC as an effective intervention to protect the heart. RIPC is assumed to produce triggers that target the heart. These triggers may be neural, hormonal or simply metabolites. If we identify the protein (e.g. enzyme) in the heart that is targeted then it may be possible to use drugs or other interventions to optimise protection through the same mechanism. Additionally, the protection induced by RIPC may be affected by disease and differences in the heart muscle. In the case of the former, the relatively ill heart muscle of a patient who requires coronary revascularisation may already be preconditioned to some extent, whereas this may not be the case for a patient with an enlarged heart who requires aortic valve replacement. In this study we plan to monitor the changes in the heart muscle associated with RIPC in patients having isolated coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) using cardiopulmonary bypass (CPB) and cardiac arrest.

Who can participate?
Patients having elective or urgent CABG and AVR using the heart lung machine and with the heart stopped.

What does the study involve?
Patients will be assigned by chance to have one of two treatments after the anaesthesia and before the operation. One group will receive RIPC, where a blood pressure cuff will be inflated for a five-minute period on one of the patients limbs (preferably the left upper arm), after which

it will be deflated for 5 minutes. This cycle of inflation followed by deflation will be performed four times in total. The other group will receive conventional treatment, which means RIPC will not be applied. The surgery and post-operative management will be carried out in the usual way and be the same for all participants. Changes in the heart muscle will be monitored in samples (left and right ventricular biopsies) collected at two times: (a) after the harvest of the mammary artery and prior to cardiopulmonary bypass and (b) at the end of the cardiac arrest. The biopsies will be analysed to compare ischaemic stress and key markers of survival signalling in the left and right ventricles, with and without RIPC, and before and after CPB and cardiac arrest. Additionally, markers of cardiac injury, inflammatory response and oxidative stress will be measured in blood samples collected at different time points throughout surgery.

What are the possible benefits and risks of participating?
If we are right in thinking that inflating and deflating a cuff around the patients limb is beneficial and protective, patients treated in this way will be less likely to have a heart injury. However, we do not know that this will happen. It is possible that patients treated conventionally may do better. We can only find out which treatment will benefit patients most by doing the study. We do not expect patients to be at higher risk. In particular, we do not expect patients receiving RIPC to have any additional pain, discomfort, distress or changes to lifestyle compared to patients who have conventional treatment.

Where is the study run from?
The study will be run by doctors and researchers at the Hammersmith Hospital and the Bristol Royal Infirmary where cardiac surgery operations are carried out.

When is the study starting and how long is it expected to run for?
The study started in February 2013 and is expected to run for 15 months.

Who is funding the study?
The study is funded by the NIHR Biomedical Research Unit (BRU) at Bristol and a personal award to Prof Gianni Angelini from the British Heart Foundation.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
3.0

Study information

Scientific Title
A two-centre randomised controlled trial investigating the effect of remote ischaemic preconditioning (RIPC) on blood and myocardial biomarkers of stress and injury-related signalling in patients having isolated coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) using cardiopulmonary bypass (CPB)

Acronym
RIsC

Study objectives
Remote ischaemic preconditioning (RIPC) has been described as a protective phenomenon in which brief cycles of inflating and deflating an arm blood-pressure cuff on a limb prior to cardiac surgery confers protection to another organ (the heart for example) against a potentially lethal reperfusion insult. Although some trials have suggested that RIPC protects the heart of paediatric and adult patients undergoing open heart surgery using heart arrest, other trials have reported that RIPC is ineffective. Reasons for the differing results may include the use of different surgical and anaesthetic techniques.

Thus, understanding the nature of any changes triggered in the heart tissue by RIPC prior to and following cardiac arrest is a key step in optimising RIPC as an effective cardioprotective intervention. RIPC is assumed to produce triggers that target the heart. If we identify the protein (e.g. enzyme) in the heart that is targeted then it may be possible to use pharmacological or other interventions to optimise protection through the same mechanism.

In this study we plan to monitor the cellular changes in the heart tissue associated with RIPC in patients having isolated coronary artery bypass grafting (CABG) or aortic valve replacement (AVR) using cardiopulmonary bypass (CPB) and heart arrest. Cellular changes will be monitored in left and right ventricular biopsies collected prior to CPB and at the end of the heart arrest. Analyses of the biopsies will allow ischaemic stress and key markers of survival signalling to be compared in the left and right ventricles, with and without RIPC and before and at the end of cardioplegic arrest. Additionally, markers of cardiac injury, inflammatory response and oxidative stress will be measured in blood samples collected at different time points throughout surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - Harrow, 18/10/2012, ref: 12/LO/1361

Study design
Interventional two-centre randomised controlled trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Cardiovascular; Subtopic: Cardiovascular (all Subtopics); Disease: Cardiovascular

Interventions
RIPC, Remote Ischaemic Pre-conditioning (RIPC) will be comprised of four 5 min cycles of right upper limb ischaemia, induced by a blood pressure cuff inflated to 200 mm Hg, with an intervening 5 min of reperfusion by deflating the cuff.

Control treatment:
This group will have anaesthesia, sternotomy, CPB and cardioplegic arrest applied in accordance with a standard protocol.

Follow Up Length: 3 month(s)

Intervention Type
Procedure/Surgery

Primary outcome(s)
Myocardial Injury; Timepoint(s): 2 pre-operatively and 6, 12, 24, 48 and 72 hours after end of cardioplegic arrest

Key secondary outcome(s))
1. Clinical endpoints measured from admission up till 3 months post-operatively
2. Inflammatory and oxidative stress measured two pre-operatively and 5 postoperatively at 6, 12, 24, 48 & 72 hours after end of cardioplegic arrest

Completion date
30/06/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 03/11/2014:
1. Age ≥18
2. Patients undergoing elective (or urgent) first-time CABG or AVR

Previous inclusion criteria:
1. Male and female, age >=40 and <85 years
2. Patients undergoing elective (or urgent) first-time CABG or AVR

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 03/11/2014:
1. Cardiogenic shock or cardiac arrest,
2. Significant peripheral arterial disease affecting upper limbs,
3. Renal failure (with a GFR < 30 ml/min/1.73m2),
4. Glibenclamide or nicorandil (as these medications may interfere with RIPC)
5. Participation in another interventional study.
6. Neither upper limb available for the intervention

Previous exclusion criteria:
1. Cardiogenic shock or cardiac arrest
2. Significant peripheral arterial disease affecting upper limbs
3. Hepatic dysfunction (Bilirubin > 20 mmol/L, Prothrombin > 2.0 ratio)
4. Pulmonary disease (FEV1 < 40% predicted)
5. Renal failure (with a GFR < 30 ml/min/1.73m2)
6. Glibenclamide or nicorandil (as these medications may interfere with RIPC)
7. Participation in another interventional study

Date of first enrolment
25/02/2013

Date of final enrolment
30/06/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College London
London
United Kingdom
W12 0NN

Sponsor information

Organisation
Imperial College London (UK)

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
British Heart Foundation (BHF) (UK) Grant Codes: CH/92027

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
NIHR (UK) - Biomedical Research Unit

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2019		Yes	No

Protocol article	protocol	23/04/2015		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes