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The effects of remote ischaemic preconditioning on coronary artery function in patients with stable coronary artery disease

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ABSTRACT

Background: Remote ischaemic preconditioning (RIPC) is a cardioprotective intervention invoking intermittent periods of ischaemia in a tissue or organ remote from the heart. The mechanisms of this effect are incompletely understood. We hypothesised that RIPC might enhance coronary vasodilatation by an endothelium-dependent mechanism.

Methods: We performed a prospective, randomised, sham-controlled, blinded clinical trial. Patients with stable coronary artery disease (CAD) undergoing elective invasive management were prospectively enrolled, and randomised to RIPC or sham (1:1) prior to angiography. Endothelial-dependent vasodilator function was assessed in a non-target coronary artery with intracoronary infusion of incremental acetylcholine doses (10^{-6}, 10^{-5}, 10^{-4} mol/l). Venous blood was sampled pre- and post-RIPC or sham, and analysed for circulating markers of endothelial function. Coronary luminal diameter was assessed by quantitative coronary angiography. The primary outcome was the between-group difference in the mean percentage change in coronary luminal diameter following the maximal acetylcholine dose (Clinicaltrials.gov identifier: NCT02666235).

Results: 75 patients were enrolled. Following angiography, 60 patients (mean ± SD age 57.5 ± 8.5 years; 80% male) were eligible and completed the protocol (n = 30 RIPC, n = 30 sham). The mean percentage change in coronary luminal diameter was −13.3 ± 22.3% and −2.0 ± 17.2% in the sham and RIPC groups respectively (difference 11.32%, 95%CI: 1.2– 21.4, p = 0.032). This remained significant when age and sex were included as covariates (difference 11.01%, 95%CI: 1.01– 21.0, p = 0.035). There were no between-group differences in endothelial-independent vasodilation, ECG parameters or circulating markers of endothelial function.

Conclusions: RIPC attenuates the extent of vasoconstriction induced by intracoronary acetylcholine infusion. This endothelium-dependent mechanism may contribute to the cardioprotective effects of RIPC.

1. Introduction

Ischaemic conditioning describes the beneficial effects of repeated cycles of ischaemia and reperfusion resulting in cardioprotection against ischaemia-reperfusion injury [1–6]. This cardioprotective strategy may be applied either directly to the heart or remotely, and before or during ischaemia-reperfusion injury [7]. Remote ischaemic preconditioning (RIPC) has been investigated in several ischaemia-reperfusion injury clinical settings, including patients with stable coronary artery disease (CAD) undergoing elective percutaneous coronary intervention (PCI) and surgical revascularisation [8–15]. RIPC is associated with a reduction in infarct size in patients following an acute myocardial infarction (MI) and after elective PCI in patients with stable CAD [8,16,17]. The mechanisms by which the cardioprotective effects of RIPC

Abbreviations: ACh, acetylcholine; ANCOVA, analysis of covariance; ANOVA, analysis of variance; ADMA, asymmetric dimethylarginine; CONSORT, Consolidated Standards of Reporting Trials; CAESAR, Consortium for preclinicAl assESsment of cARdioprotective therapies; CAD, coronary artery disease; ECG, electrocardiogram; IMR, index of microcirculatory resistance; IL-6, interleukin-6; MPO, myeloperoxidase; MI, myocardial infarction; NO, nitric oxide; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RIPC, remote ischaemic preconditioning; t-PA, tissue plasminogen activator; vWF, Von Willebrand factor.

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act are incompletely understood [18]. The effects of RIPC on health outcomes in patients with acute ST-segment elevation myocardial infarction (STEMI) are currently being assessed in two large phase 3 clinical trials in Europe (CONDI-2 NCT01857414 and ERIC NCT02342522).

Three components of the RIPC stimulus may be defined: signal generation from the tissue or organ remote from the heart, transmission of the cardioprotective signal to the heart, and the mechanism of the cardiac response [19]. The molecular mechanisms and signal transduction of the conditioning phenomena in the heart have been described as involving extracellular trigger molecules, intracellular protein kinase activation and the mitochondria as the end-effector [20]. The signal transduction from the distant organ/tissue to the heart is incompletely understood, but likely involves both neural and hormonal pathways [21–24].

Since coronary artery function has pivotal importance for regulating myocardial perfusion, we hypothesised that RIPC would have favourable effects on coronary artery endothelial dysfunction. Endothelial dysfunction is prevalent in patients with atherosclerotic CAD and associated with adverse health outcomes [25–27]. This mechanism could potentially contribute to the cardioprotective effects of RIPC through enhanced coronary artery blood flow leading to improved myocardial perfusion following ischaemia-reperfusion injury. Studies of RIPC have identified endothelial-dependent responses that potentially implicate endothelial cell activation in mediating enhanced coronary blood flow and cardioprotective effects [28–31]. Conversely, we are not aware of experimental evidence for an effect of RIPC on endothelial-independent vascular function.

Our first aim was to determine whether RIPC might affect coronary artery function in vivo in patients with stable CAD. Should this be the case, we next aimed to determine the contribution of endothelium-dependent and -independent function on the observed responses. Our second aim was to assess whether circulating molecules reflecting endothelial cell vasodilatory and fibrinolytic function might be associated with a RIPC-mediated effect on coronary artery function. Thirdly, since a neural hypothesis implicates activation of the autonomic nervous system via one or more pathways [32–34], we aimed to assess cardiac conduction using the surface electrocardiogram (ECG) [35].

2. Methods

2.1. Trial design

We performed a prospective, randomised, sham-controlled, blinded (physician, researcher) clinical trial.

2.2. Study population

Patients undergoing elective invasive coronary angiography for investigation of stable CAD were enrolled and provided written informed consent. The study was approved by the National Research Ethics Service (reference 10/S0704/52). The ClinicalTrials.gov identifier is NCT02666235. Patients were eligible if, following initial coronary angiography, there was a main epicardial coronary artery suitable for coronary reactivity testing (either an angiographically normal coronary artery, or an artery with minimal plaque burden and without an epicardial diameter stenosis ≥40%). Exclusion criteria were MI <2 weeks, previous coronary artery bypass grafting, second or third degree atrioventricular block, and inability to provide informed consent.

2.3. Setting

The study took place between July 2011 and March 2016 in a regional cardiac centre. Potentially eligible participants were identified by screening clinically-indicated referrals for invasive coronary angiography.

2.4. Informed consent

Eligible patients were sent a Patient Information Sheet (PIS) before attending hospital for the clinically-indicated coronary angiogram. The PIS had been approved by the local ethics committee and written informed consent was obtained on the ward before the procedure.

2.5. Randomisation, implementation and blinding

Randomisation took place immediately after obtaining verbal consent using a web-based computer tool with a concealed random allocation sequence provided by the independent clinical trials unit and implemented by the researcher (D.C.). Randomisation was on a 1:1 basis between RIPC or sham immediately prior to the invasive procedure. The study was conducted according to CONSORT guidelines for clinical trials.

2.6. Intervention

2.6.1. Remote ischaemic preconditioning

RIPC was performed according to a standard protocol involving intermittent inflation of an arm sphygmomanometer cuff for 5 min periods at 200 mm Hg, separated by a 5-minute rest interval, and repeated successively on 4 occasions [8].

2.6.2. Sham procedure

The sham procedure involved cuff placement alone without inflation.

Following the RIPC or sham procedure, patients underwent angiography and coronary reactivity testing within 1 h.

2.7. Primary and secondary endpoints

The protocol for end-point acquisition and assessment is illustrated in Fig. 1.

2.8. Assessment of physiological responses of the coronary artery and microcirculation

All vasodilator therapy apart from sublingual glyceryl trinitrate was withheld for 24 h prior to coronary reactivity testing. Coronary angiograms were acquired using cardiac catheter laboratory X-ray (Innova®, GE Healthcare; Chicago, Illinois) and information technology equipment (Centricity®, GE Healthcare).

Reactivity testing of the coronary circulation, including the epicardial artery and its microvascular branches, included assessments of endothelial-dependent vasodilation following intracoronary infusion of graded doses of acetylcholine, and then assessment of endothelial-independent vasodilation following intracoronary administration of glyceryl trinitrate.

Endothelial function testing was performed using a standardised protocol by an operator blinded to the group allocation [36]. A 3 French infusion catheter (Cook Medical; Bloomington, Indiana) was placed in the proximal-to-mid segment of the epicardial coronary artery. A control intracoronary infusion of a 0.9% saline (2 ml over 2 min) was followed by intracoronary acetylcholine in incremental concentrations (10^{-6}, 10^{-5}, 10^{-4} mol/l). The infusion rate of acetylcholine was 2 ml/min giving approximate doses of 0.364, 3.64, and 36.4 μg, respectively.

Following each intracoronary infusion, an assessment of patient symptoms, 12 lead ECG, and angiography using identical imaging projections (Innova®, GE Healthcare) and information technology equipment (Centricity®, GE Healthcare) were performed. Acetylcholine infusion was discontinued if: i) second or third degree atrioventricular block occurred; ii) there was angiographic evidence of severe epicardial vasospasm (reduction in the epicardial diameter ≥75%); iii) there was evidence of severe microvascular spasm (angina and ST-segment deviation occurring in the absence of epicardial coronary diameter change ≥75%) [37]. If these criteria were not present, we administered the next dose of acetylcholine. Following a second wash-out infusion of 0.9% saline for a period of 2 min, endothelial-independent vasodilation was tested with an intracoronary bolus of glyceryl trinitrate (400 μg).

2.9. Invasive coronary angiography and analysis

Quantitative coronary angiography (QCA) was performed by three experienced cardiologists (P.C., A.B., C.B.) in the Glasgow Angiography Core Laboratory, using proprietary automated edge-detection software (Medis QAngio XA, Leiden, Netherlands). The angiographic images were calibrated to the coronary guide catheter size. The end-diastolic angiographic image demonstrating the best luminal contrast opacification was chosen for analysis. The coronary segment distal to the infusion catheter or the coronary segment demonstrating the most marked diameter change in the main epicardial vessel was analysed to determine the mean coronary artery luminal diameter for the selected segment. Analysts were blinded to the group assignment.

2.10. Mechanistic evaluation of circulating biomarkers of endothelial function

Venous blood was obtained from the contralateral arm pre- and then within 1 h post-RIPC or sham procedure. Venous blood was analysed for circulating molecules associated with endothelial vasodilator function (myeloperoxidase (MPO), interleukin-6 (IL-6), von Willebrand factor (vWF), asymmetric dimethylarginine (ADMA)) and endothelial fibrinolytic function (tissue plasminogen activator (t-PA)). Laboratory methods are described in the online-only supplement. Laboratory technicians were blinded to the group allocation.