Effect of Remote Ischemic Preconditioning on Acute Kidney Injury in Nondiabetic Patients Undergoing Coronary Artery Bypass Graft Surgery: A Secondary Analysis of 2 Small Randomized Trials

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Background: Novel treatment strategies are required to reduce the development of acute kidney injury (AKI) in patients undergoing cardiac surgery. In this respect, remote ischemic preconditioning (RIPC), a phenomenon in which transient nonlethal ischemia applied to an organ or tissue protects another organ or tissue from subsequent lethal ischemic injury, is a potential renoprotective strategy.

Study Design: Secondary analysis of 2 randomized trials.

Setting & Participants: 78 consenting selected nondiabetic patients in a university teaching hospital undergoing elective coronary artery bypass graft (CABG) surgery recruited to 2 previously reported randomized studies.

Intervention: RIPC consisted of three 5-minute cycles of right forearm ischemia, induced by inflating a blood pressure cuff on the upper arm to 200 mm Hg, with an intervening 5 minutes of reperfusion, during which time the cuff was deflated. The control consisted of placing an uninflated cuff on the arm for 30 minutes.

Outcomes: AKI measured using Acute Kidney Injury Network (AKIN) criteria, duration of hospital stay, in-hospital and 30-day mortality.

Results: Numbers of participants with AKI stages 1, 2, and 3 were 1 (3%), 3 (8%), and 0 in the intervention group compared with 10 (25%), 0, and 0 in the control group, respectively ($P = 0.005$). The decrease in AKI was independent of the effect of concomitant aortic valve replacement and cross-clamp times, which were distributed unevenly between the 2 groups.

Limitations: Retrospective analysis of data. More patients in the RIPC group underwent concomitant aortic valve replacement with CABG; although we have corrected statistically for this imbalance, it remains an important confounding variable.

Conclusions: RIPC induced using transient forearm ischemia decreased the incidence of AKI in nondiabetic patients undergoing elective CABG surgery in this retrospective analysis. A large prospective clinical trial is required to study this effect and clinical outcomes in patients undergoing cardiac surgery.
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INDEX WORDS: Remote ischemic preconditioning; transient limb ischemia; coronary artery bypass graft surgery; acute kidney injury.

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Acute kidney injury (AKI) affects up to 30% of patients undergoing cardiac surgery, with 1%-2% of patients going on to require dialysis therapy.[1] Its presence is associated with significant morbidity and mortality, such that even after adjustment for patient comorbid conditions and surgical complications, the presence of AKI requiring dialysis therapy increases the risk of death by 8 times in this patient group.[2] Furthermore, changes >0.5 mg/dL in serum creatinine level after cardiac surgery also contribute to a significant increase in

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mortality at 30 days postsurgery.[3] A variety of treatment strategies have been investigated in an effort to decrease AKI incidence in patients undergoing cardiac surgery; however, on the whole, these have been disappointing (reviewed in[1]). Therefore, novel treatment strategies are required to decrease AKI incidence, preserve kidney function, and improve clinical outcomes in patients undergoing cardiac surgery.

In this regard, remote ischemic preconditioning (RIPC) may offer a novel noninvasive and virtually cost-free treatment strategy for decreasing AKI incidence in patients undergoing cardiac surgery (reviewed by Hausenloy and Yellon[4]). RIPC describes the phenomenon in which transient nonlethal ischemia and reperfusion applied to one organ or tissue protects another organ or tissue from a subsequent episode of lethal ischemia and reperfusion. Recent proof-of-concept clinical studies have shown that RIPC using transient ischemia and reperfusion of the lower limb can preserve kidney function in patients undergoing elective endovascular[5] or open surgical repair[6] of an abdominal aortic aneurysm. Whether RIPC is able to decrease AKI incidence in patients undergoing elective coronary artery bypass graft (CABG) surgery remains to be determined.

METHODS

Patient Selection

Ethics approval from the local University College London Hospital/University College London Ethics Committee was obtained. This study is a retrospective analysis of nondiabetic patients selected from 2 cohorts of patients undergoing CABG surgery who originally were recruited to investigate whether RIPC would decrease perioperative myocardial injury.[7,8] Although the first study of 57 patients (30 control, 27 RIPC) included both diabetic (24 patients; 23 control and 22 RIPC) and nondiabetic participants undergoing CABG total,[7] the latter study (45 patients: 23 control and 22 RIPC) included only nondiabetic patients. Therefore, to ensure uniformity, we included only the nondiabetic patients from the first study in this analysis, as shown in Fig 1. Family physician and medical notes for 78 nondiabetic patients (38 RIPC and 40 control) were analyzed retrospectively to investigate the effect of RIPC on kidney function, duration of hospital stay, and in-hospital mortality.

Intervention: RIPC Protocol

RIPC consisted of three 5-minute cycles of right upper-limb ischemia induced by a blood pressure cuff placed on the right upper arm and inflated to 200 mm Hg, with an intervening 5 minutes of reperfusion during which time the cuff was deflated. Control patients had an uninflated cuff placed on the right upper arm for 30 minutes. The RIPC protocol was applied after anesthetic induction and before the start of surgery. As such, patients and cardiac surgeons were blinded to treatment allocation.

All nondiabetic patients previously randomly assigned to RIPC or control in 2 previously reported single-blind random-

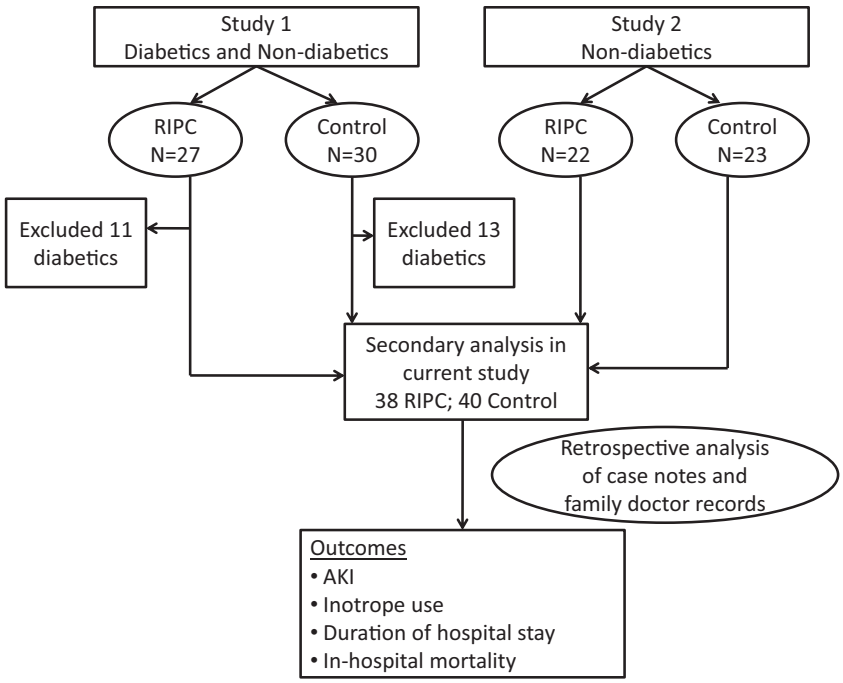

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of patients included in the present study. Study 1 and study 2 refer to previously reported studies[7,8] from which data were retrospectively analyzed for outcomes in the present study. Study 1 was registered at ClinicalTrials.gov as study number NCT00397163. Abbreviations: AKI, acute kidney injury; RIPC, remote ischemic preconditioning.