Remote Ischemic Preconditioning Prevents Deterioration of Short-Term Postoperative Cognitive Function After Cardiac Surgery Using Cardiopulmonary Bypass: Results of a Pilot Investigation

Judith A. Hudetz, PhD, Kathleen M. Patterson, PhD, Zafar Iqbal, MD, Sweeta D. Gandhi, MD, and Paul S. Pagel, MD, PhD

Objective: **Remote ischemic preconditioning (RIPC) exerts neuroprotective effects in models of cerebral ischemia-reperfusion injury. The authors tested the hypothesis that RIPC decreases the incidence of postoperative delirium and prevents deterioration of short-term postoperative cognitive function in isoflurane-fentanyl-anesthetized patients undergoing cardiac surgery using cardiopulmonary bypass (CPB).**

Design: **Randomized, blinded, single-center pilot investigation.**

Setting: **Veterans Affairs Medical Center.**

Participants: **Thirty age- and education-matched men $\geq$ 55 years of age undergoing elective coronary artery or valve surgery using CPB. Fifteen nonsurgical patients also were enrolled.**

Interventions: **RIPC was produced after induction of anesthesia using 4 cycles of brief (5 minutes) upper extremity ischemia (tourniquet inflation to 200 mmHg) interspersed with 5-minute periods of reperfusion (tourniquet deflation).**

Measurements and Main Results: **The Intensive Care Delirium Screening Checklist was used to assess delirium before and each day after surgery for as many as 5 consecutive days. Recent verbal and nonverbal memory and executive functions were assessed before and 1 week after surgery using a standard neuropsychometric test battery or at 1-week intervals in nonsurgical controls. The Geriatric Depression and the Hachinski Ischemia scales were used to identify the presence of clinical depression and vascular dementia, respectively. No differences in delirium scores were observed between RIPC and control groups ($p = 0.54$). Baseline neurocognitive scores were similar in patients with versus without RIPC in all 3 cognitive domains. Significant declines in performance on 2 nonverbal memory tests (figure reconstruction and delayed figure reproduction; $p = 0.001$ and $p = 0.003$, respectively) and 1 verbal memory test (delayed story recall; $p = 0.0004$) were observed 1 week after surgery in patients who were not treated with RIPC. There were no changes in performance of measures of executive function in this group. In contrast, performance on all cognitive tests was unchanged after compared with before surgery in patients receiving RIPC. At least a 1-standard deviation decline from baseline in cognitive performance was detected in figure reconstruction, delayed figure reproduction, immediate story recall, and delayed story recall in patients who were not exposed to RIPC. The incidence of at least a 1-standard deviation decline in neuropsychometric tests was observed in significantly fewer (1 *v* 9; $p < 0.0001$) patients with versus without RIPC treatment based on composite Z-scores. Overall cognitive performance after surgery was better in patients treated with versus without RIPC ($p = 0.002$). Clinical depression and vascular dementia were not detected in either group.**

Conclusion: **The results of this pilot investigation indicated that RIPC prevented deterioration of short-term postoperative cognitive function but were unable to detect any difference in delirium in isoflurane-fentanyl-anesthetized patients undergoing cardiac surgery using CPB.**

KEY WORDS: remote ischemic preconditioning, postoperative cognitive impairment, delirium, isoflurane, cardiac surgery, cardiopulmonary bypass, neuroprotection

ISCHEMIC PRECONDITIONING of one tissue is capable of protecting an unrelated tissue from the damage produced by a subsequent prolonged episode of ischemia and reperfusion.[1] This remarkable transfer of protection from 1 preconditioned tissue to another is termed "remote ischemic preconditioning" (RIPC)[2] and has been demonstrated in the brain,[3,4] heart,[5] kidney,[6] liver,[7] stomach,[8] pancreas,[9] and skeletal muscle.[10] Brief, repetitive ischemia of the upper or lower extremity is most often used to produce RIPC.[11] The phenomenon has been well documented in the human heart[12–16] and is currently the subject of 2 large multicenter randomized, controlled clinical trials in patients undergoing cardiac surgery.[17,18] The mechanisms responsible for transmission of the RIPC signal from 1 organ to another remain incompletely understood, but most likely involve a combination of modulation of leukocyte function, changes in inflammatory cytokine expression and activity, altered autonomic nervous system traffic, and release of circulating factors including nitrite.[1,19]

RIPC also exerts neuroprotective effects in animal models of cerebral ischemia. RIPC was shown to enhance recovery of cortical neuronal activity,[20] conserve cerebral oxygen tension,[21] and reduce cortical injury[4] after hypothermic circulatory arrest. These data support the tantalizing hypothesis that RIPC may be useful for reducing the incidence and severity of perioperative stroke or for mitigating the more subtle changes in neurologic function (eg, delirium, cognitive impairment) that often are observed in patients undergoing cardiac surgery using cardiopulmonary bypass. This contention was evaluated in 2 recent studies,[22,23] both of which yielded disappointing results, as RIPC failed to attenuate postoperative cognitive impairment (PCI) in patients undergoing cardiac surgery with or without cardiopulmonary bypass.[22,23] It is important to note, however,

From the Anesthesia Service, the Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin.

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Address reprint requests to Paul S. Pagel, MD, PhD, Clement J. Zablocki Veterans Affairs Medical Center, Anesthesia Service, 5000 W. National Avenue, Milwaukee, WI 53295. E-mail: pspagel@mcw.edu

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that these negative results may not have been because of a lack of efficacy of RIPC per se, but rather, to the presence of a propofol-based anesthetic[1] that was used in both studies [22,23] Indeed, RIPC-induced myocardial protection did not occur consistently when propofol was used as part of the anesthetic technique because the intravenous anesthetic interfered with signal transducer and activator of transcription 5 (STAT5),[24,25] a crucial element in RIPC signaling.[26] STAT5-mediated signaling occurs in the brain,[27] and it appears likely that propofol anesthesia also may inhibit RIPC-induced neuroprotection through a similar mechanism. Volatile anesthetics have been shown to produce neuroprotective effects in experimental models of ischemic brain injury.[28,29] Accordingly, the authors tested the hypothesis that RIPC decreases the incidence of postoperative delirium and prevents deterioration of short-term postoperative cognitive function in isoflurane-fentanyl-anesthetized patients undergoing cardiac surgery using cardiopulmonary bypass.

METHODS

The Institutional Review Board of the Clement J. Zablocki Veterans Affairs Medical Center approved the study. All subjects provided written informed consent. Thirty age- and education-balanced men (older than 55 years of age) scheduled for elective coronary artery bypass graft surgery (CABG), mitral or aortic valve repair or replacement, or CABG plus valve surgery using cardiopulmonary bypass were enrolled. Exclusion criteria included previously documented cognitive deficits, cerebrovascular accident, upper extremity vascular disease or claudication, and planned harvest of the radial artery for conduit use during CABG. Patients with hepatic impairment (aspartate aminotransferase or alanine aminotransferase more than twice the upper normal limit) and chronic renal insufficiency (creatinine greater than 2 mg/dL) also were excluded.

Closed envelopes containing a note that allocated each patient to receive RIPC or sham upper extremity occlusion and reperfusion were used for randomization (Latin square design). One hour before surgery, a closed envelope was drawn and opened by the attending anesthesiologist. After anesthetic induction and endotracheal intubation, RIPC was produced in selected patients using 4 cycles of brief (5 minutes) upper extremity ischemia by inflating a tourniquet to 200 mmHg interspersed with 5-minute periods of reperfusion during which the tourniquet was deflated. Repetitive brief occlusion and reperfusion were completed before aortic cannulation and initiation of cardiopulmonary bypass in all patients. A tourniquet that remained deflated was placed on an upper extremity of patients who did not receive RIPC (control).

Each patient underwent delirium and neurocognitive function evaluation, depression screening, and neurologic assessment before surgery. Delirium was monitored and reassessed up to 5 consecutive days after surgery by 2 independent qualified examiners. If the 2 examiners did not reach agreement on the diagnosis, a third examiner was asked to evaluate the patient. Neurologic status, cognitive functions, and depression were assessed 1 week after surgery or at time of hospital discharge, whichever occurred first. Fifteen age- and education-matched nonsurgical controls were included for statistical purposes to account for possible practice effects of the readministered cognitive tests. Study personnel performing the pre- and postoperative neurocognitive and delirium assessments were blinded to group assignment.

The Intensive Care Delirium Screening Checklist (ICDSC) was used to assess delirium. This instrument includes altered level of consciousness, inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance, and symptom fluctuation and is based on Diagnostic and Statistical Manual-IV criteria and features of delirium.[30] Raters assessed the study subjects and completed the checklist based on data from the previous 24 hours. The 8 items were scored as 1 (present) or 0 (absent) for a total of 8 points. A score of 4 or more points indicated a positive screen for delirium.[30]

A brief neuropsychometric battery was used to assess cognitive changes. The test battery tested verbal memory, nonverbal memory, and executive functions because these domains are known to be affected after cardiac surgery.[31,32] The test battery was designed to be completed in less than 1 hour before and after surgery to avoid fatigue. Two parallel forms of the tests were used for all tests except for the Stroop and Digit Span tests, which are not vulnerable to practice effects. Story memory (subtest of the Rivermead Behavioral Memory Test[33]) was used to assess recent verbal memory. This test measures the ability to learn and recall a narrative story immediately and after a brief delay (maximum score of 21). The Brief Visual Memory Test Revised[34] was used to test recent nonverbal memory on three sequential trials (maximum score 12 points/trial) and includes figure construction (immediate recall of geometric shapes across trials) and delayed figure reproduction. Backward Digit Span[35], Semantic Fluency[36], Phonemic Fluency[37], and the Color-Word Stroop Test (3rd part)[38] were used to test executive functions. Semantic and phonemic fluency are subtests of the Delis-Kaplan Executive Function System[39] that examine executive functions related to language. Semantic fluency measures executive speed of word generation using semantic cues such as identifying all the "fruits and vegetables" (form A) or "animals in the zoo" (form B) that the patient is able to produce in 1 minute. The obtained score is the number of appropriate words generated within the time interval. Phonemic fluency measures executive speed of word generation using phonetic cues to produce words that start with the letter "S" (form A), "P" (form B), or "B" (form C) in 1 minute. The score is the number of appropriate words generated within the time interval. Digit span is a subtest of the Wechsler Adult Intelligence Scale-Third Edition[35] that measures attention span, concentration, and working memory. The score for backward digit span is the number of correct digits repeated accurately backward. The Color-Word Stroop Test (3rd part)[38] assesses executive functions of inhibition, selective attention, mental speed, and interference susceptibility. This test presents a list of color words printed in an incongruous color and requires that the examinee name the correct color while ignoring the word. The score is the number of colors correctly identified in 1 minute.

The Geriatric Depression Scale 15-item version (GDS-15)[40] is an affirmative-negative questionnaire designed to detect the presence of depression in older adults. The obtained score is the number of items endorsed (maximum score 15). A score of 9 or greater on this scale indicates the presence of depression.

Hachinski Ischemia Scale (maximum score 18) was used to identify vascular dementia.[41] A score of 4 or greater indicates the presence of vascular dementia.

Each patient received intravenous midazolam (1-3 mg) and fentanyl (50-150 μg) for conscious sedation. Intravenous and radial artery catheters were inserted using local anesthesia (1% lidocaine). Supplemental oxygen (2-4 L/min per nasal cannula) was provided. A central venous catheter, or, when clinically indicated, a pulmonary artery catheter, was inserted using local anesthesia (1% lidocaine) under sterile conditions through the right internal jugular vein using ultrasound guidance. Anesthesia was induced using intravenous etomidate (0.3 mg/kg), fentanyl (3 to 5 μg/kg), and rocuronium (1 mg/kg), and was maintained using inhaled isoflurane (end-tidal concentration of 0.5%-1.0%) in 100% oxygen, fentanyl (2-3 μg/kg/h in divided doses), midazolam (1-3 mg), and rocuronium (0.05 mg/kg) titrated to effect using train-of-four monitoring. A comprehensive transesophageal echocardiography examination was performed in all patients. Intravenous hydromorphone (2 mg) or morphine (10 mg) was administered for postoperative analgesia after separation from cardiopulmonary bypass.