# Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: Five-year follow-up of a randomized trial

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**Objective:** In a randomized trial of 223 patients undergoing coronary artery surgery with cardiopulmonary bypass, we have reported a neuroprotective effect of mild hypothermia. To determine whether the beneficial effect of mild hypothermia was long-lasting, we repeated the psychometric tests in 131 patients after 5 years.

**Methods:** Patients were cooled to 32°C during aortic crossclamping and then randomized to rewarming to either 34°C or 37°C, with no further rewarming until arrival in intensive care unit. Cognitive function was measured preoperatively and 1 week and 5 years postoperatively with a battery of 11 psychometric tests interrogating verbal memory, attention, and psychomotor speed and dexterity.

**Results:** Patients who had greater cognitive decline 1 week after surgery showed poorer performance 5 years later. The magnitude of cognitive decline over 5 years was modest. The incidence of deficits defined as a 1 standard deviation [SD] decline in at least 1 of 3 factors was not different between temperature groups. Fewer patients in the hypothermic group had deficits that persisted over the 5 years, but this difference did not attain statistical significance (RR = 0.64, $P = .16$).

**Conclusions:** The effect of surgery on cognitive function observed early after surgery is an important predictor of cognitive performance 5 years later. Although there was evidence of a neuroprotective effect of mild hypothermia early after surgery in the original cohort, the results after 5 years were inconclusive. In general, the magnitude of cognitive changes over 5 years was modest. We believe that further trials investigating the efficacy of mild hypothermia in patients having cardiac surgery are warranted.

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Funded by the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research.

Received for publication May 2, 2006; revisions received July 4, 2006; accepted for publication Sept 11, 2006.

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J Thorac Cardiovasc Surg 2007;133:1206-11

0022-5223/$32.00



doi:10.1016/j.jtcvs.2006.09.112

A decline in cognitive performance after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) can be demonstrated in the majority of patients.[1] Diminished cognitive function after CABG has been shown to be associated with diminished quality of life 5 years afterward.[2] Although the cause of this decline is not known, brain ischemia resulting from microemboli or hypoperfusion is believed to play a role.[3] Mild hypothermia (lowering brain temperature by 2°C to 5°C) during or even after ischemia is a highly effective neuroprotective strategy and is now recommended after out-of-hospital cardiac arrest.[4] We[5] have previously reported a clinical trial in which patients undergoing

**Abbreviations and Acronyms**
CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
RR = relative risk
SD = standard deviation

CABG were randomized to rewarming at the end of CPB to 37°C or 34°C. We found that there was a reduction in the incidence of cognitive deficits 1 week after surgery in the hypothermic group (relative risk [RR] 0.77, $P = .048$). The performance of the hypothermic group on one test of psychomotor speed and dexterity (Grooved Pegboard) was still highly significantly superior to that of the control group 3 months after surgery, suggesting a permanent benefit. Newman and associates[6] observed that patients who exhibited a significant cognitive decline early after CABG improved when tested again at 6 weeks and 6 months but 5 years later again showed significant impairment compared with patients who did not show an early postoperative decline. This suggests that the perioperative injury causing the decline has long-lasting effects and also suggests that an intervention that prevents the early decline may have long-lasting beneficial effects. We recalled patients from our original study 5 years after surgery and repeated the psychometric test battery. We wished to determine whether the cognitive decline documented 1 week after surgery persisted and whether the beneficial effect of mild hypothermia was long-lasting.

## Materials and Methods

Between August 1995 and February 1998, patients 60 years or older undergoing elective or urgent CABG who had no history of any neurologic event, no major comorbidity, and no impediment to completing psychometric testing were invited to participate in the original trial. Institutional Research Review Board approval and informed consent was obtained for both the original trial and the 5-year follow-up.

The protocol is given in detail in the original publication.[5] In brief, patients underwent CABG with CPB using membrane oxygenators and 43-$\mu$m arterial filters. All were cooled to 32°C (nasopharyngeal temperature) during application of the aortic crossclamp. When rewarming commenced, a sealed opaque envelope containing the treatment assignment was opened. The perfusionists then rewarmed the patients to a nasopharyngeal temperature of either 34°C or 37°C, taking care not to raise the temperature of the blood leaving the pump-oxygenator above 37.5°C. The patients' temperature was held constant until separation from CPB. Upon arrival in the intensive care unit, warming blankets were applied and all patients reached 36°C within 5 hours postoperatively.

### Measurement of Neurocognitive Function and Quality of Life

Learning efficiency and memory consolidation were evaluated with a verbal list–learning procedure (Buschke Selective Reminding administration and scoring). Alternate forms were used to reduce practice effects. Attention span was evaluated with the Wechsler Adult Intelligence Scale—Revised Digit Span. Psychomotor speed and dexterity were measured by Trails A and B, Grooved Pegboard, and the Symbol Digit Modalities Test (oral administration). From these tests we calculated the following measures: (1) Buschke Total Learning Free Recall; (2) Buschke consistent long-term retrieval; (3) Buschke long-term retrieval; (4) Buschke long-term storage; (5) Buschke Delayed Recall; (6) Digit Span Forward; (7) Digit Span Backward; (8) Trails A; (9) Trails B (maximum score = 300 seconds); (10) Grooved Pegboard (dominant hand, maximum score = 300 seconds); and (11) Symbol Digit Modalities Test. Patients were tested within the 4 weeks before surgery and then approximately 1 week, 3 months (not reported here), and 5 years after surgery. Both the psychometrist and the patient were unaware of the treatment assignment.

### Statistical Methods

We analyzed the psychometric test results both as continuous outcomes and as dichotomous outcomes. For each of the 11 psychometric test scores, analysis of covariance was used to assess the effect of temperature assignment and surgery. We used the 5-year score as the dependent variable, the baseline score and the 1-week postoperative score (effect of surgery) as covariates, and the treatment group as a fixed independent variable. For all tests a higher score indicates improved performance except for the timed tests of speed and dexterity (Trails A, Trails B, and Pegtime), where increased score indicates poorer performance. To facilitate the categorical analysis, we combined the 11 psychometric tests into 3 cognitive domains using factor analysis with orthogonal rotation as described by Newman and colleagues.[6] The scoring coefficients used to generate the domain scores for the 3 visits were determined from the baseline scores of the entire 223 patients who were enrolled in the original trial. This method reduced the 11 scores into 3 variables that are uncorrelated. The 3 factors accounted for 80% of the variance present in the test battery and, in composition, resembled the 3 domains presented in our original publication: verbal memory, psychomotor speed and dexterity, and attention. The scores were adjusted so that an increase in score always indicates better performance. A composite score, intended to represent overall cognitive performance, was formed by summing the three individual factors. A patient was deemed to have had a cognitive deficit if one or more factor scores decreased by at least 1 SD. The incidence of deficits was compared between groups by an uncorrected $\chi^2$ test.

## Results

Of the 223 patients who were randomized, 194 completed 1-week postoperative testing. Ninety-two patients in the normothermic and 81 in the hypothermic group survived, of whom 66 and 65, respectively, completed the 5-year testing. Reasons for loss to follow-up in the normothermic and hypothermic groups, respectively, were as follows: death 8,