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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See related editorial on page 1133.

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-μm 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 χ^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,

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TABLE 1. Preoperative characteristics

Characteristic	Completers 37°C (n = 66)	Completers 34°C (n = 65)	Non-completers 37°C (n = 46)	Non-completers 34°C (n = 46)
Age at operation (y)	67 ± 5	68 ± 5	69 ± 6	68 ± 6
Male sex	59 (89)	54 (83)	36 (78)	40 (87)
LV ejection fraction <35%	10 (15)	12 (18)	11 (24)	13 (28)
Education				
Grade 8 or less	19 (29)	25 (38)	14 (30)	15 (33)
Grade 9-12	22 (33)	17 (26)	17 (37)	15 (33)
College/university	25 (38)	23 (35)	15 (33)	16 (35)
CCS				
1 and 2	17 (26)	18 (28)	11 (24)	11 (24)
3	37 (56)	42 (65)	27 (59)	24 (52)
4	10 (15)	4 (6)	8 (17)	10 (22)
Unknown	2 (3)	1 (2)	0 (0)	1 (2)
NHYA				
I	44 (67)	45 (69)	28 (61)	31 (67)
II	16 (24)	10 (15)	8 (17)	5 (11)
III	6 (9)	10 (15)	7 (15)	9 (20)
IV	0 (0)	0 (0)	3 (7)	1 (2)
Diabetes mellitus	18 (26)	16 (24)	9 (20)	10 (22)
Urgent cases	8 (12)	8 (12)	7 (15)	10 (22)
Previous CABG	4 (6)	9 (14)	7 (15)	8 (17)
Creatinine (mmol/L)	89 ± 20	87 ± 19	92 ± 19	94 ± 23

Plus–minus values are mean ± SD; others are No. (%). *LV*, Left ventricular; *CCS*, Canadian Cardiovascular Society angina classification; *NYHA*, New York Heart Association functional classification; *CABG*, coronary artery bypass grafting.

13; too ill to participate 6, 2; refused 10, 7; unable to contact 10, 7. The retention rate was therefore 131 (68%) of 194 or 131 (76%) of 173 survivors. The mean (±SD) times between surgery and the follow-up in the normothermic and hypothermic groups were 5.5 ± 0.42 (range 4.5-6.8) and 5.5 ± 0.46 (range 4.4-6.7) years, respectively.

The preoperative characteristics of the patients are presented in Table 1. There was a trend for patients with poor left ventricular function (P = .091) and New York Heart Association class III and IV (P = .058) to be lost to follow-up; however, there was no imbalance across temperature groups. Intraoperative and postoperative characteristics (Table 2) were similar in the two temperature groups except for the design variable, temperature.

The mean scores and mean change scores for the neuropsychometric tests and factors are presented in Table 3. The baseline scores of the 66 patients assigned to normothermia and the 65 assigned to hypothermia were well balanced except for Digits Forward, in which the normothermic group performed significantly better (P = .038). Those lost to follow-up (data not shown) had preoperative scores that overall seemed slightly inferior to the completers; however, the difference was significantly different only for the Buschke Delayed Recall (P = .014). More important, among those lost to follow-up, preoperative scores in the hypothermic group were not significantly different from those in the normothermic group.

Among the 5-year participants, 2 tests showed significantly less decline 1 week postoperatively in the hypothermic group: time to complete the Grooved Pegboard and Digits Backward. We examined the effect of preoperative test score, 1-week postoperative score, and temperature assignment on cognitive performance 5 years postoperatively using analysis of covariance. For all 11 tests, a lower baseline score predicted lower performance 5 years later ($P < .01$). For 9 of 11 tests, lower 1 week postoperative score (independent of baseline score) predicted lower performance 5 years later ($P < .01$, except for Pegtime and Trails A, P = .075 and .331, respectively). In no case was there a significant effect of temperature on the 5-year test scores.

Patients exhibiting a decrease of at least 1 SD in one or more of the three factors at the 1-week postoperative visit were deemed to have a cognitive deficit. In the original cohort of 194 patients who were tested both preoperatively and 1 week postoperatively, the incidence of deficits was 46

TABLE 2. Surgical characteristics

Treatment	Completers 37°C (n = 66)	Completers 34°C (n = 65)	Completers *P* value	Non-completers 37°C (n = 46)	Non-completers 34°C (n = 46)	Non-completers *P* value
CPB time (min)	85 ± 27	86 ± 26	.834	80 ± 26	89 ± 27	.141
Crossclamp time (min)	48 ± 18	46 ± 14	.479	43 ± 17	49 ± 15	.084
Grafts	3.2 ± 0.9	3.1 ± 0.7	.202	2.9 ± 0.7	3.2 ± 0.9	.193
Glucose* (mmol/L)	6.6 ± 1.3	6.5 ± 1.4	.783	6.3 ± 1.3	6.5 ± 1.5	.482
Hematocrit* (mmol/L)	0.25 ± 0.04	0.25 ± 0.04	.514	0.25 ± 0.04	0.25 ± 0.04	.571
Nasopharyngeal temperature at end of CPB (°C)	36.9 ± 0.3	34.2 ± 0.5	<.001	36.8 ± 0.3	34.1 ± 0.2	<.001
Intraoperative inotrope infusions	3 (4.6)	9 (13.9)	.065	8 (17.4)	8 (17.4)	1.0
Temperature on arrival in recovery room (°C)	35.4 ± 0.6	33.6 ± 0.5	<.001	35.2 ± 0.6	33.5 ± 0.5	<.001

Plus–minus values are mean ± SD. *P* value refers to the comparison between temperature assignments. *CPB*, Cardiopulmonary bypass. *Both glucose and hematocrit were measured just before rewarming commenced: 1 mmol/L glucose = 18.02 mg/dL.

TABLE 3. Neuropsychometric test scores

	Normothermia (n = 66)			Hypothermia (n = 65)		
		Change from preop			Change from preop	
	Preop	1 wk	5 y	Preop	1 wk	5 y
Verbal memory						
BFR	41.1 ± 8.8	2.7 ± 8.3	1.2 ± 8.5	41.1 ± 8.8	2.7 ± 9.0	0.7 ± 8.7
BCLTR	20.5 ± 12.2	2.9 ± 14.7	1.8 ± 12.7	20.1 ± 2.6	3.8 ± 13.3	1.3 ± 12.2
BLTR	26.3 ± 12.7	4.3 ± 3.4	2.5 ± 13.4	26.3 ± 12.9	4.0 ± 3.1	2.2 ± 3.3
BLTS	28.8 ± 13.0	5.0 ± 14.1	2.6 ± 14.3	29.7 ± 12.7	3.4 ± 12.4	1.9 ± 4.1
BDR	6.4 ± 2.8	−0.2 ± 2.4	−0.5 ± 2.2	6.5 ± 2.7	−0.2 ± 3.0	−0.4 ± 2.3
Speed						
Trails A	39.9 ± 11.6	1.8 ± 14.1	2.9 ± 1.8	38.7 ± 11.5	2.2 ± 13.8	6.5 ± 19.0
Trails B	103.7 ± 9.2	14.7 ± 46.5	14.1 ± 43.6	104.3 ± 46.7	12.7 ± 39.0	24.2 ± 47.8
Pegtime*	87.5 ± 20.7	17.4 ± 32.8	13.7 ± 21.6	88.2 ± 17.0	6.7 ± 17.3	14.7 ± 30.7
SDMT	43.8 ± 10.6	−4.6 ± 8.2	−2.9 ± 5.8	42.8 ± 11.1	−3.5 ± 6.4	−3.4 ± 6.8
Attention						
Digfor†	8.2 ± 2.3	−0.4 ± 1.6	−0.6 ± 1.5	7.3 ± 2.5	−0.2 ± 2.0	−0.3 ± 2.0
Digback*	6.8 ± 2.7	−1.1 ± 2.1	−0.1 ± 2.2	6.2 ± 2.4	−0.3 ± 2.0	−0.1 ± 1.9
Factor 1 (verbal memory)	0.04 ± 0.99	0.41 ± 1.02	0.24 ± 1.00	0.10 ± 1.01	0.30 ± 1.04	0.23 ± 1.01
Factor 2 (speed)	−0.01 ± 0.99	−0.71 ± 1.14	−0.59 ± 0.92	0.07 ± 0.96	−0.46 ± 0.85	−0.83 ± 1.49
Factor 3 (attention)†	0.27 ± 1.01	−0.16 ± 0.84	0.00 ± 0.69	−0.16 ± 1.00	−0.04 ± 0.84	0.16 ± 0.84
Composite Cognitive Index	0.30 ± 1.80	−0.47 ± 1.21	−0.35 ± 1.07	0.02 ± 1.75	−0.20 ± 1.11	−0.44 ± 1.33

All scores presented as mean ± SD. *Preop*, Preoperative; *1 wk*, early postoperative score − preoperative score; *5 y*, 5-year score − preoperative score; *BFR*, Buschke free recall; *BCLTR*, Buschke consistent long-term retrieval; *BLTR*, Buschke long-term retrieval; *BLTS*, Buschke long-term storage; *BDR*, Buschke delayed recall; *Pegtime*, Grooved Pegboard; *Digfor*, Digit Span Forward; *Digback*, Digit Span Backward; *SDMT*, Symbol Digit Modalities Test. *$P < .05$ at 1-week change, normothermia versus hypothermia. †$P < .05$ at preoperative, normothermia versus hypothermia.

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(46%) of 100 in the normothermic group and 30 (32%) of 94 in the hypothermic group (RR 0.69, $P = .045$), suggesting a neuroprotective effect of mild hypothermia very similar to that determined in our earlier report using different criteria.[5] In the 131 patients who completed 5-year testing, the incidence of deficits 1 week postoperatively was 30 (45%) of 66 in the normothermic group and 22 (34%) of 65 in the hypothermic group ($P = .175$). After 5 years, the incidences were 29 (44%) of 66 and 27 (42%) of 65 in the normothermic and hypothermic groups, respectively ($P = .781$).

To estimate the magnitude of cognitive decline experienced by the patients over the 5-year period, we calculated the mean change scores for each test and tested whether the change was significantly different from 0. We did the same selecting only patients who had a decline of 1 SD or more 1 week postoperatively in any of the 3 factors to quantitate the change in patients who showed an adverse effect of surgery. Standardized scores (z-scores) are presented to provide a common scale for comparisons between the different tests (Table 4). Even in the group defined as having early postoperative deficits, no test decreased by as much as 1 SD over the 5 years.

With the composite cognitive index at the 5-year follow-up used as the dependent variable, a stepwise multiple regression indicated that significant independent predictors of poor performance 5 years after surgery included lower baseline score, lower early postoperative score, poor left ventricular function, higher preoperative creatinine level, and less education. Temperature assignment was not significant. The model explained 76% of the variance in the data; baseline score alone accounted for 65%.

Last, we wished to determine whether the effect of temperature assignment on the number of patients who had deficits 1 week postoperatively persisted over the 5 years: that is, we tested whether there was a difference between temperature groups in the proportion of patients demonstrating deficits at both 1 week and 5 years. For completeness, we present 3 different criteria for defining deficits. Using the criterion of 1 SD decrease in at least 1 factor, the incidence was 19 (29%) of 66 in the normothermic group and 12 (18%) of 65 in the hypothermic group; the RR associated with hypothermia was 0.64 (95% confidence interval [CI], 0.34–1.21, $P = .164$). Using the criterion of 1 SD decrease in factor 2 (the most sensitive to surgery, see Table 3), the incidence was 10 (15%) of 66 in the normothermic group and 4 (6%) of 65 in the hypothermic group; the RR was 0.41 (CI, 0.13–1.23, $P = .096$). Using the criterion of 1 SD decrease in the composite cognitive index, the incidence was 12 (18%) of 66 in the normothermic group and 5 (8%) of 65 in the hypothermic group; the RR was 0.42 (CI, 0.16–1.13, $P = .074$). More patients in the hypothermic

TABLE 4. Change over 5 years, standardized scores

	All completers (n = 131)	Patients with deficits (n = 52)
Verbal memory		
BFR	0.11	−0.05
BCLTR	0.13	0.00
BLTR	0.18*	0.04
BLTS	0.17	0.04
BDR	−0.16*	−0.34*
Speed		
Trails A	−0.39†	−0.54*
Trails B	−0.39†	−0.55†
Pegtime	−0.73†	−0.93†
SDMT	−0.30†	−0.38†
Attention		
Digfor	−0.19†	−0.43†
Digback	−0.03	−0.16

Negative change indicates worsened performance. *BFR*, Buschke free recall; *BLTR*, Buschke long-term retrieval; *BLTS*, Buschke long-term storage; *BDR*, Buschke delayed recall; *Pegtime*, Grooved Pegboard; *Digfor*, Digit Span Forward; *Digback*, Digit Span Backward. $*P < .05$ change score significantly different from 0. $†P < .01$ change score significantly different from 0.

group who did not have deficits 1 week postoperatively demonstrated new deficits when tested 5 years later. For this reason, there was a similar proportion of patients with deficits in each group after 5 years.

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Discussion

We have completed a 5-year follow-up of a randomized trial of the neuroprotective effect of mild hypothermia in patients undergoing CABG with CPB. In the original study group a significant effect was seen 1 week postoperatively. This effect was no longer significant in the 131 patients who completed the 5-year follow-up. The analysis of group mean data indicates that both baseline and early postoperative cognitive performance, but not temperature assignment, are important independent determinants of cognitive function 5 years later. The fact that early postoperative performance is correlated with 5-year performance suggests that the impact of surgery has long-lasting effects on cognitive outcome. Overall, however, the average decline in cognitive function over the 5-year period was small. An analysis of patients who had persistent cognitive deficits (1 week postoperatively as well as 5 years later) was suggestive but not conclusive of a long-term beneficial effect of mild hypothermia.

We found a highly significant and consistent effect of early postoperative decline on long-term cognitive outcome. The fact that we could demonstrate this on 9 of 11 raw test scores makes the present results unambiguous and confirms similar findings by others.[6,7] This suggests that an intervention that reduces early decline would be expected to have long-lasting beneficial effects.

We, along with Newman[6] and Selnes[8] and their associates, observed only small decrements in cognitive function 5 years after CABG. Even the cohort defined as having had a significant decline 1 week after surgery demonstrated only modest decline. Longitudinal studies of healthy elderly persons[9,10] show no change in cognitive function when tested yearly over periods longer than 5 years, in part because of practice effects. It would be expected that our patients with advanced atherosclerotic disease and less practice effect after 5 years, even without surgery, would have more decline than healthy subjects. Selnes and coworkers[11] have reported the longest follow-up study (3 years) comparing CABG patients and nonsurgical controls with atherosclerosis and found few differences between the groups. However, group means reported in the above studies combine the results of individuals whose scores improve or stay the same with a smaller number of individuals who show a decline that may be important. This effect is better described with a categorical approach,[12] as has also been done in the present study.

More patients in the hypothermic group had new deficits late after surgery, when the treatment strategy could have no effect. A reduction in the proportion of patients who had deficits 1 week postoperatively that persisted over the 5 years may be a more sensitive measure of a long-lasting benefit of hypothermia. The observed reduction in incidence of persistent deficits with hypothermia, although not statistically significant, should, we believe, encourage further testing of this neuroprotective strategy for this population of patients.

Several studies have found no benefit of hypothermic CPB on early postoperative neuropsychologic outcome of CABG.[13-16] Two studies were suggestive but not conclusive of a beneficial effect.[17,18] A common characteristic of these studies is rewarming of all patients before separation from CPB, often heating blood to temperatures exceeding 37°C. Thus, the duration of exposure to a beneficial effect of hypothermia was brief and these patients were likely exposed to the deleterious effects of cerebral hyperthermia during rewarming.[19] The importance of extending the period of hypothermia as long as possible after injury is well established in the laboratory[20] and is a feature of positive clinical studies.[4] Although our trial maintained a temperature gradient between groups longer than other trials, this gradient did diminish after separation from CPB. Also, the normothermic group became mildly hypothermic. It is possible that if the groups could have been kept at 34°C and 37°C longer, the treatment may have been more efficacious. We are currently testing this hypothesis. We[21] have recently demonstrated that extending hypothermia into the early postoperative period is safe for these patients.

Loss to follow-up is a limitation of this study. However, retention was better than in similar studies,[6-8] and the data collected on the patients lost to follow-up show no evidence of a selective process that may have biased the study sample. Both groups of patients experienced rewarming after a period of hypothermia during aortic crossclamping. The 34°C group was rewarmed less. Although care was taken not to exceed perfusion (oxygenator outlet) temperatures of greater than 37.5°C, it is possible that rewarming was a greater stress to the 37°C group.

Our test battery contained the core tests recommended by a consensus committee[22] and examined a broad range of brain functions. The use of cutoffs to categorize patients as having deficits is recommended by some[6,12] but avoided by others.[7,11,23] Comparing group means is appropriate if one assumes that all patients in a group are a sample of the same population, that is, had a similar degree of injury during surgery. The categorical approach assumes that patients showing a decline greater than the cutoff have had a significant injury whereas others have not. Both approaches help to describe the data, and we have chosen to present both to the reader.

Conclusions

We have found that the degree of decline in cognitive function observed 1 week after CABG with CPB is an important predictor of cognitive performance 5 years later. Hypothermia reduced the incidence of deficits in the 194 patients who were tested before and 1 week after surgery and therefore might be expected to have a long-term effect. In the 131 who completed 5-year testing, there was some evidence suggestive of a neuroprotective effect of mild hypothermia, but the results were inconclusive. In general, the cognitive changes observed were modest. We believe that further trials investigating the efficacy of mild hypothermia extending into the period after CABG with CPB are warranted.

We acknowledge the expert assistance of Dawn Houbraken, RN, Sharon Finlay, RN, Denyse Winch, RN, and Geri Wells.

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