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Prospective Randomized Trial of Normothermic versus *Hypothermic Cardiopulmonary Bypass on Cognitive Function after Coronary Artery Bypass Graft Surgery*

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Background: **Despite significant advances in cardiopulmonary bypass (CPB) technology, surgical techniques, and anesthetic management, central nervous system complications occur in a large percentage of patients undergoing surgery requiring CPB. Many centers are switching to normothermic CPB because of shorter CPB and operating room times and improved myocardial protection. The authors hypothesized that, compared with normothermia, hypothermic CPB would result in superior neurologic and neurocognitive function after coronary artery bypass graft surgery.**

Methods: **Three hundred patients undergoing elective coronary artery bypass graft surgery were prospectively enrolled and randomly assigned to either normothermic (35.5–36.5°C) or hypothermic (28–30°C) CPB. A battery of neurocognitive tests was performed preoperatively and at 6 weeks after surgery. Four distinct cognitive domains were identified and standardized using factor analysis and were then compared on a continuous scale.**

Results: **Two hundred twenty-seven patients participated in 6-week follow-up testing. There were no differences in neurologic or neurocognitive outcomes between normothermic and hypothermic groups in multivariable models, adjusting for covariable effects of baseline cognitive function, age, and years of education, as well as interaction of these with temperature treatment.**

Conclusions: **Hypothermic CPB does not provide additional central nervous system protection in adult cardiac surgical patients who were maintained at either 30 or 35°C during CPB.**

CARDIAC surgery with cardiopulmonary bypass (CPB) is associated with a predictable incidence of central nervous system dysfunction that accounts for significant morbidity and mortality.[1–3] Embolic events, changes in cerebral blood flow, global hypoperfusion, cerebral reperfusion injury, and a CPB-triggered whole body inflammatory response represent possible mechanisms. Elderly patients are more susceptible to cognitive impairment and stroke after cardiac surgery than others.[4] Thus, with the increase in the percentage of elderly patients undergoing coronary artery bypass graft (CABG) surgery, there has been a parallel increase in the incidence of stroke and neurocognitive dysfunction.[5,6] Importantly, overall mortality after cardiac surgery has decreased over the past 20 yr, but adverse events attributed to neurologic deficits have increased.[7] This may be a result of the fact that the vast improvements in myocardial protection during cardiac surgery occurred, but similar advances in neurologic protection have not.

In the last decade, several investigators have revived the use of systemic normothermia with warm cardioplegic solution during CPB.[8–10] These investigators noted a higher rate of spontaneous defibrillation after cross-clamp removal, as well as a trend toward a lower rate of myocardial infarction and reduced use of the intraaortic balloon pump in the "warm heart" patients. Thus, systemic normothermia with warm cardioplegia represents a safe technique, suitable for high-risk patients undergoing cardiac surgery.[10] However, the abandonment of the potentially neuroprotective action of hypothermia could affect cerebral protection during CPB. In this prospective, randomized study, we tested the hypothesis that hypothermia during CPB reduces the incidence and severity of postoperative neurocognitive dysfunction.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

After institutional review board approval (Duke University Medical Center, Durham, NC) and written informed consent were obtained, 300 patients undergoing elective CABG were enrolled in the study. Patients with history of cerebrovascular disease with residual deficits, uncontrolled hypertension, alcoholism, psychiatric illness, renal disease (creatinine concentration > 2 mg/dl), and active liver disease were excluded. Pregnant women and patients with less than a seventh-grade education were also excluded. Patients were randomly assigned before surgery to normothermic (35.5–36.5°C) CPB systemic perfusion ("warm group") or hypothermic

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(28–30°C) CPB systemic perfusion ("cold group"). Both groups received intermittent hypothermic (8°C) antegrade blood cardioplegic solution for myocardial protection during CPB. Investigators performing the preoperative and postoperative assessments were blinded to the temperature assignment of each patient. Only the physicians directly involved with the intraoperative care of these patients were aware of group assignment.

Neurologic Testing

Complete neurologic examinations were performed by a Neurology Fellow preoperatively and on days 3–5 postoperatively. Neurologic function was rated based on the following: (1) clinical diagnosis of stroke or encephalopathy; (2) a single global rating with seven possible responses; and (3) by means of the Western Perioperative Neurologic Scale (WPNS). Stroke was defined as the fulfillment of any of the following criteria: (1) new motor or sensory deficits of the face or upper and lower extremities (not attributable to peripheral lesions); (2) impaired speech; (3) visual disturbances; or (4) encephalopathy defined as altered level of consciousness or confusion (not attributable to pharmacologic or metabolic causes) as the result of diffuse cerebral dysfunction, diagnosed from clinical judgment using data from neurologic examination. The global neurologic score provided the examiner's impression of the patient's general neurologic state: normal, minimal, mild, moderate, serious, severe, or vegetative. The WPNS is designed to detect and quantify anatomically discrete neurologic dysfunction. It includes 14 specific items in eight domains: mentation, speech, cranial nerve (two items), motor (four items), cerebellum–sensation (three items), reflexes (two items), and gait. Each item is scored from 0 (severe deficit) to 3 (normal), for a total possible score of 42.

For assessment of neurologic change, the amount of change in WPNS scores from before surgery to after surgery was used as a numeric measure of neurologic outcome. Discrete binary (*i.e.*, yes–no) neurologic outcomes included the following: (1) decline of two or more points on the WPNS, representing either mild decrease in performance on two items or significant decrease on one item; and (2) clinical evidence of new stroke, encephalopathy, and postoperative neurologic deficit on neurologic evaluation.

An overall "adverse neurologic outcome" variable was defined as the occurrence of any of the following discrete outcomes: (1) decline of two or more levels in the seven-level global assessment; (2) new stroke at discharge; (3) new encephalopathy at discharge; or (4) postoperative neurologic changes suggestive of a stroke (table 1). Stroke was a clinical outcome and not defined by computed tomography scans or magnetic resonance imaging.

Table 1. Adverse Neurologic Outcome

Decrease of two or more levels in the seven-level global assessment
New stroke at discharge
New encephalopathy at discharge
Postoperative neurologic changes suggestive of stroke

Neuropsychologic Testing

A neurocognitive battery was administered the day before surgery and at 6 weeks postoperatively. Cognitive functioning was assessed by several methods[11]:

1. The Short Story module of the Randt Memory Test requires subjects to recall the details of a short story immediately after it has been read to them (immediate) and after a 30-min delay;
2. The Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised Test requires subjects to repeat a series of digits that have been orally presented to them both forward and, in an independent test, in reverse order;
3. The Digit Symbol subtest of the Wechsler Adult Intelligence Scale–Revised Test is a paper-and-pencil task that requires subjects to reproduce, within 90 s, as many coded symbols as possible in blank boxes beneath randomly generated digits according to a coding scheme for pairing digits with symbols;
4. The Modified Visual Reproduction Test from the Wechsler Memory Scale measures short- and long-term figural memory and requires subjects to reproduce from memory several geometric shapes both immediately and after a 30-min delay[12];
5. The Trail Making Test (Trails) (part B) requires subjects to connect, by drawing a line, a series of numbers and letters in sequence (*i.e.*, 1-A-2-B) as quickly as possible.

Anesthetic and Surgical Techniques

Patients were premedicated with 0.1 mg/kg diazepam and 0.1 mg/kg methadone orally 90 min before induction. Induction and maintenance of anesthesia was achieved with a continuous infusion of midazolam and fentanyl.[13] Supplemental isoflurane (0.5–1.0%) was used as required to maintain heart rate and mean blood pressure within 25% of the preinduction values. Pancuronium was administered to achieve and maintain neuromuscular paralysis. The perfusion apparatus consisted of a Cobe CML oxygenator (COBE Chem Labs, Lakewood, CO), a Sarns 7000 max pump (Sarns Inc., 3M Inc., Ann Arbor, MI), and Pall SP 3840 arterial line filter (Pall Biomedical Products Co., Glen Cove, NY). Nonpulsatile perfusion was maintained at 2–2.4 $l \cdot min^{-1} \cdot m^{-2}$. The pump was primed with crystalloid solution (0.9% normal saline) designed to achieve a hematocrit of 0.18 or higher during extracorporeal circulation. Packed erythrocytes were added when necessary to maintain the

desired hematocrit. All patients were perfused during CPB through an ascending aortic cannula. Arterial carbon dioxide tension was maintained throughout CPB at 35–40 mmHg (uncorrected for temperature), with the arterial oxygen tension maintained at 150–250 mmHg. Mean arterial pressure was maintained between 50 and 90 mmHg during CPB using intravenous phenylephrine or nitroprusside as required.

Patients enrolled in the normothermic group received a perfusate inflow temperature of 36°C and were actively rewarmed to a nasopharyngeal temperature of 37°C before separation from CPB using an inflow temperature of 38°C. The hypothermic group received an inflow temperature of 28°C and was also rewarmed to a nasopharyngeal temperature of 37°C after cross-clamp removal and before discontinuation of CPB per institutional guidelines. Maximal perfusate temperature was maintained at 38°C. Myocardial protection was achieved in both groups with cardioplegia delivered at 8°C. Myocardial temperature was maintained at 20°C or less during the period of aortic cross-clamping. Nasopharyngeal temperature and mean arterial pressure were measured each minute during CPB and recorded automatically using the Arkive® Information Management System (Arkive IMS Inc., San Diego, CA). Nasopharyngeal temperature measurements during the rewarming period were summarized as follows: (1) peak temperature; (2) duration (minutes) of temperature greater than 37°C; and (3) area under the curve for the period during which the mean temperature was greater than 37°C.

Statistical Analysis

Baseline and demographic characteristics were compared using the Fisher exact test for categoric variables and the *t* test or Wilcoxon rank sum test for numeric variables. Significance was assessed at a two-tailed α of 0.05.

To assess neurocognitive decline over time while minimizing the potential for neurocognitive testing overlap, a factor analysis with orthogonal rotation was performed on the eight baseline neurocognitive measures obtained from the five neurocognitive instruments for the entire population.[14,15] This method finds the commonality (overlap in testing) among the set of raw scores and constructs a smaller set of independent factor scores, each representing a separate domain of cognitive function. The four factors represent the following cognitive domains: (1) verbal memory and language comprehension, short-term and delayed; (2) figural or visual memory, short-termed and delayed; (3) attention and concentration; and (4) visuospatial orientation, psychomotor processing speed, and attention. Factor scores for both baseline and 6-week cognitive function were calculated using the factor loadings and weights from the baseline analysis. In this manner, the factors (cognitive domains) were identified at preoperative baseline testing and remained consistent for the 6-week test period.

An overall (summary) cognitive function score at each test period was determined by adding together the independent factor scores. A cognitive change score (cognitive index) was calculated by subtracting the baseline from the 6-week score for each of the factors and for the overall score, thus representing a continuous measure of cognitive assessment. In addition, a binary cognitive deficit outcome event was defined as a decline in performance of 1 SD or more in any of the independent factors (domains). The baseline summary score was used to control for baseline cognitive function in multivariable models.

The effect of temperature treatment on 6-week change in cognitive function scores was investigated with linear regression models. The effect of temperature treatment on the occurrence of cognitive deficit at 6 weeks was investigated with logistic regression models. Although the analysis of neurocognitive performance as a continuous measure is more sensitive to improvement, the analysis of neurocognitive deficit as a dichotomous measure captures only serious decline. As a first step in all analyses, the unadjusted association between treatment and outcome (cognitive function scores and cognitive deficit as dependent variables) was tested either by a simple linear correlation or Fisher exact test. Then multivariable models were used for both linear and logistic regression models to test and adjust for covariable effects of baseline cognitive function, age, years of education, diabetes, left ventricular ejection fraction, as well as the interactions of these with temperature treatment. Nonsignificant covariables were dropped stepwise from the models, starting with interactions.

For neurologic assessment, the amount of change at predischarge in WPNS scores was calculated by subtracting the baseline score from the predischarge score. These change scores were used as numeric measures of neurologic outcome. Discrete binary (*i.e.*, yes–no) neurologic outcomes included:

1. decline of two or more points on the WPNS;
2. clinical evidence of new stroke, encephalopathy, and postoperative neurologic deficit on neurologic evaluation:
   - decline of two or more levels in the seven-level global assessment;
   - new stroke at discharge;
   - new encephalopathy at discharge; or
   - postoperative neurologic changes suggestive of a stroke.

An overall adverse neurologic outcome variable was defined as the occurrence of any of the discrete outcomes above. The effect of temperature treatment on predischarge neurologic outcome was investigated in a way similar to the cognitive outcome, with linear regres-

Table 2. Demographic Characteristics of Warm and Cold Groups

Variable	Warm (%, mean)	Cold (%, mean)	*P* Value
ASA physical status IV	72	70	0.77*
History of HTN	56	63	0.35*
Diabetes	26	21	0.43*
Race (white)	88	89	0.99*
Sex (male)	79	74	0.44*
Age	60	61	0.59†
LVEF (%)	55	56	0.62†
Years of education	13	12	0.25†
No. of grafts	3	3	0.86†
Cross-clamp time (min)	54	53	0.30†
CPB time (min)	104	104	0.62†

* Using the Fisher exact test. † *P* value for Wilcoxon Rank-Sum Test comparing groups.

ASA = American Society of Anesthesiologists; HTN = hypertension; LVEF = left ventricular ejection fraction; CPB = cardiopulmonary bypass.

sion models on the WPNS change scores and logistic regression models on the binary neurologic outcomes.

Missing Data

Many statistical analysis methods, including factor analysis, require that patients with incomplete data be dropped from analysis. Rather than losing all psychometric data on patients who were missing only a few scores from a test battery, missing data were imputed using "place holder" values that do not affect group mean change scores but allow the rest of the patient's data to be used in analysis. Patients missing both baseline and 6-week scores on a test were given the group mean for baseline, to which the mean change for that test was added for the 6-week score. Patients missing only the 6-week score were assigned their own baseline plus the mean change for that test for a 6-week score. Similarly, if only the baseline score was missing, it was imputed from the patient's 6-week score minus the mean change for that test. No imputation was performed for patients who did not return for testing at 6 weeks or who were missing more than two of the eight scores from a testing period. Patients whose 6-week scores were missing because of death or stroke were given worst possible scores on 6-week tests. Data were analyzed both with and without these scores included. Patients who were not treated as assigned (because of the surgeon's decision during the operation to change the CPB temperature) were analyzed as randomized (intention to treat) and in a separate follow-up analysis were analyzed based on treatment received.

Results

A total of 300 patients undergoing elective CABG surgery were enrolled in the study: 298 completed preoperative testing, and 227 completed 6-week postoperative testing. Table 2 shows that the warm and cold groups were similar with respect to preoperative and operative characteristics. Despite the randomization, the preoperative neurocognitive tests revealed slightly poorer performance in the cold group than the warm group (table 3).

One hundred forty-nine patients were randomized to the warm CPB group, while 151 patients received hypothermic CPB. As intended, patients in the cold group had a lower mean nasopharyngeal temperature during CPB (30.4 ± 1.4°C) than patients in the warm group (35.1 ± 1.3°C) ($P < 0.01$; table 4, fig. 1). During CPB, because of surgical considerations, four patients (3%) in the cold group were kept at a temperature greater than 35°C, and 13 patients (9%) in the warm group were cooled to less than 32°C during CPB. These protocol violations occurred because of surgical requirements, *i.e.*, the operating surgeon requested the temperature to facilitate the operation. During the late phase of rewarming during CPB, the patients in the cold group had a higher mean peak temperature (37.6 ± 0.5°C *vs.* 37.0 ± 0.7°C; $P < 0.001$), an increased mean duration of temperature greater than 37°C (28.2 ± 23.4 min *vs.* 15.5 ± 23.8 min; $P < 0.001$), and a higher mean temperature area greater than 37°C (11.4 ± 12.2°C-min *vs.* 5.5 ± 11.7°C-min; $P < 0.001$) than patients in the warm group.

Baseline neurocognitive tests were completed in 147 patients in the warm group and 151 patients in the cold group. There were 32 patients in the warm group and 39 patients in cold group who missed the 6-week neurocognitive assessment after CABG and were therefore excluded (table 5). Two patients in the cold group were excluded from analysis for missing more than two of the eight scores from a testing period. Thus, at 6 weeks after CABG, 117 patients in the warm group and 110 patients in the cold group completed neurocognitive testing. A total of only 35 scores of 5,250 used in analysis (0.67%) were imputed. Factor analysis yielded four factors representing separate domains of cognitive function and accounting for 83% of the variance in the test battery: factor 1, verbal memory and language comprehension, short-term and delayed; factor 2, figural or visual memory, short-term and delayed; factor 3, attention and concentration; and factor 4, visuospatial orientation, psychomotor processing speed, and attention. The overall incidence of cognitive deficit (≥ 1 SD decline in any of four independent factors) was 39.3% (46 of 117) in the warm group and 39.1% (43 of 110) in the cold group ($P = 0.99$). There were no statistically significant differences between warm and cold groups in incidence or severity of cognitive decline at 6 weeks (table 6). The mean change in total cognitive index at 6 weeks was 0.341 ± 0.871 in the warm group and 0.348 ± 0.975 in the cold group ($P = 0.89$, univariate Wilcoxon rank sum test). Multivariate analyses of the incidence and severity of cognitive change, controlling for baseline cognitive

Table 3. Raw Scores for Neurocognitive Test Battery by Treatment Group at Baseline and 6 Weeks Postoperatively

	Warm				Cold			
	Baseline		6 Weeks		Baseline		6 Weeks	
Cognitive Test	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Randt Immediate	7.9	2.4	8.2	2.2	7.4	2.3	7.8	2.3
Randt Delayed*	6.5	2.7	6.8	2.4	5.8	2.6	6.4	2.7
Digit Symbol	41	12.6	45	13.9	39.7	12.3	42.5	13.1
Trail-making B	168.3	255.8	150	234.4	165.8	191.8	149	139.8
Digit Span Forward	7.8	2.3	7.7	2.4	7.4	2.5	7.4	2.4
Digit Span Backward	5.8	2.2	6	2.5	5.4	2.1	5.7	2.3
Figural Memory Immediate	6.9	3.2	7.4	3.1	6.6	3.5	6.9	3.3
Figural Memory Delayed	5.5	3.1	5.8	3.2	5	3.1	5.5	3.3

* Wilcoxon rank-sum $P = 0.0501$ for comparison of groups at baseline.

function, age, years of education, diabetes, and left ventricular ejection fraction, revealed similar results.

Neurologic outcome based on preoperative and postoperative neurologic examination was determined in 136 patients in the warm group and 134 patients in the cold group. The incidence of any adverse neurologic event was 14.7% (20 of 136) in the warm group compared with 13.4% (18 of 134) in the cold group ($P = 0.86$). Two strokes occurred in each group (1.32% in the cold group and 1.34% in the warm group; $P = 0.7$).

None of the patients enrolled in the warm group died or required insertion of intraaortic balloon pump. Of the total number of subjects enrolled in the cold group, three patients (1.9%) died, and two (1.3%) required insertion of intraaortic balloon pump. The difference between groups was not significant ($P = 0.25$ and 0.50 respectively). One patient in each group experienced postoperative cardiac arrest ($P = 0.99$). None of the patients enrolled in the study returned to the operating room for graft revision or uncontrolled bleeding. Results from all secondary analyses, including the analysis of groups as treated (instead of as randomized), did not differ from the primary analysis.

Discussion

Our hypothesis that hypothermic CPB has neuroprotective effects reflected in a reduction of decreased cognitive function was not proven. Thus, the major finding of our study is that hypothermic CPB as practiced (at our institution with a temperature difference of 4.7°C) makes no difference in cognitive performance.

Hypothermia is used in heart, brain, and other organ protection during CPB. During hypothermic conditions, the rate of myocardial use of adenosine triphosphate and creatine phosphate is decreased secondary to a reduction in electromechanical and basal metabolic activity.[16] Moderate hypothermia has been routinely used during CPB with the hope of providing organ protection, although mechanisms for this purported protection remain unclear. During hypothermic conditions, the rate of myocardial use of adenosine triphosphate is decreased secondary to a reduction in electromechanical and basal metabolic activity.

In the ischemic brain, moderate hypothermia reduces cerebral metabolic rate,[17] blocks release of glutamate,[18] reduces calcium influx,[19] hastens recovery of protein synthesis,[20] diminishes membrane-bound protein kinase C activity,[21] slows time to onset of depolarization,[22] reduces formation of reactive oxygen species,[23] suppresses nitric oxide synthase activity,[24] and inhibits spontaneous depolarizations.[25] Consistent with this, either intraischemic or sustained postischemic moderate (or mild) hypothermia provide lasting reduction of brain injury in innumerable laboratory models of acute brain injury. Despite these findings, there remains no human evidence derived from prospective, randomized, appropriately powered studies that either mild or moderate hypothermia serves as a neuroprotectant against acute brain injury, although such studies are currently ongoing.[26] Several smaller studies have identified interesting trends toward neuroprotection in humans suffering from closed head injury or undergoing cerebral aneurysm

Table 4. Physiologic Variables During Cardiopulmonary Bypass

	Cold		Warm		
	Mean	SD	Mean	SD	*P**
TempNP	30.44	1.4	35.13	1.27	< 0.0001
MAP	67.11	13.36	70.04	12.35	0.1318
Hematocrit	21.92	4.21	21.92	3.61	0.9897
Pa_{O_2}	237.7	39.37	231.13	49.54	0.3075
Pa_{CO_2}	35.75	3.4	36.59	3.36	0.0811
Sa_{O_2}	97.23	0.91	97.21	0.76	0.8147
CVP	4.29	4.91	3.86	3.92	0.521
Pv_{CO_2}	45.39	3.99	46.15	2.85	0.126
Pv_{O_2}	38.91	6.93	37	6.43	0.0468
Sv_{O_2}	70.14	8.46	66.29	8.39	0.0016

Values reported are after cross-clamping the aorta.

* *P* value for *t* test comparing groups.

TempNP = nasopharyngeal temperature; MAP = mean arterial pressure; Pa_{O_2} = radial arterial P_{O_2}; Pa_{CO_2} = radial arterial P_{CO_2}; Sa_{O_2} = radial artery saturation; CVP = superior vena caval pressure; Pv_{CO_2} = venous reservoir P_{CO_2}; Pv_{O_2} = venous reservoir P_{O_2}; Sv_{O_2} = venous reservoir saturation.

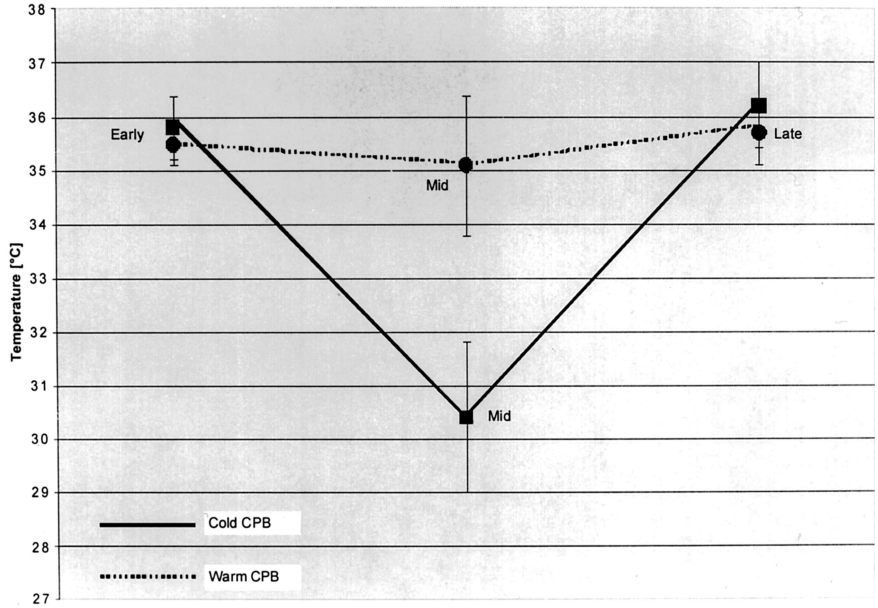

Fig. 1. Mean temperature and SD in the early, middle, and late phases of cardiopulmonary bypass (CPB) by study group.

surgery, but sustained improvement in outcome measures did not reach statistical significance.[26,27]

There are, however, potential limitations to hypothermia efficacy during CPB. Although hypothermia decreases overall cellular metabolism, oxygen delivery is likewise decreased as the result of a leftward shift in the oxygen–hemoglobin dissociation curve.[28] In addition, as previously discussed, a reduced temperature reduces cerebral blood flow. Hemodilution also reduces oxygen-carrying capacity of the blood, and the total oxygen delivery to the tissue may be diminished. Moreover, during obligate systemic rewarming, because nasopharyngeal temperatures underestimate jugular venous temperatures, the central nervous system could be exposed to supranormal temperatures, potentially accelerating ischemic cerebral injury.[29–32] Other deleterious effects of hypothermic CPB include postbypass redistribution hypothermia,[33] an increased risk of blood loss and transfusion requirements,[34] reversible platelet dysfunction,[35] impaired leukocyte and T-cell function,[36] and increased metabolic rate and myocardial oxygen consumption as a result of shivering.[37]

The concept of warm heart surgery was partly proposed to reduce or prevent these harmful effects of hypothermia.[38] Several studies have subsequently attempted to assess the effect of normothermic *versus* hypothermic CPB on cerebral outcome in cardiac surgical patients (table 7). Although these investigators have looked at similar patient populations, results have been conflicting. Martin *et al.*,[39] in a series of 1,001 patients, and Mora *et al.*,[40] using data from a subgroup (n = 138) of this patient population, reported a significantly increased rate of neurologic dysfunction in patients undergoing warm (> 35°C) CPB compared with cold (< 28°C) CPB. In the study by Mora *et al.*,[40] the patients enrolled in the normothermic group were older than those in the hypothermic group, thus predisposing them to a greater potential for neurologic dysfunction.[40] Similarly, the warm group in the study by Martin *et al.*[39] experienced longer periods of aortic cross-clamping. Moreover, temperature management during CPB was not well controlled, and active rewarming of the normothermic patients during all of CPB to bladder temperatures between 35 and 37°C might have achieved brain temperatures greater than 37°C.

Alternatively, many investigators have reported no relation between perfusion temperature and neurologic outcome.[41–45] These studies are also limited by the use of deliberate hyperthermia (39°C perfusion temperature) during rewarming,[41] the use of hypothermic temperatures (34–35°C) in the warm group,[42] a significantly higher duration of CPB and cross-clamp time in the cold group,[43] the use of retrospective chart review for assess-

Table 5. Reason for the Missed 6-Week Neurocognitive Assessment

Reason	Patients in Warm Group	Patients in Cold Group
Transportation	1	8
Interest	9	9
Stress	0	2
Health	9	11
Family	1	1
Time	4	1
No contact	3	2
Died	0	3
No show	1	0
Other	4	2

Transportation = too difficult to get to the hospital for testing; interest = patient not interested in repeating testing; stress = patient found testing too stressful; health = patient did not feel well enough to participate; family = family responsibilities prevented testing; time = patient too busy; no contact = unable to contact patient for follow-up; no show = patient failed to keep testing appointment; other = patient expressed other reason for not participating.

Table 6. Mean, Standard Deviation, and Median of Continuous Cognitive Function Factor Scores by Treatment Group

Cognitive Score	Warm (n = 117)			Cold (n = 110)			Wilcoxon *P* Value
	Mean	SD	Median	Mean	SD	Median	
Total factor score at baseline	0.432	1.885	0.699	0.039	1.912	0.167	0.0452
Total factor score 6 weeks	0.773	1.856	0.633	0.387	1.985	0.294	0.0770
Total 6-week factor change	0.341	0.871	0.278	0.348	0.975	0.293	0.8946
Change in factor 1 at 6 weeks	0.084	1.180	0.159	0.190	1.089	0.188	0.3985
Change in factor 2 at 6 weeks	0.156	0.967	0.149	0.093	0.962	0.033	0.7181
Change in factor 3 at 6 weeks	−0.018	0.721	0.0	0.014	0.855	0.041	0.5885
Change in factor 4 at 6 weeks	0.119	0.459	0.045	0.051	0.459	0.019	0.2503

Factor 1 = verbal memory and language comprehension, short-term and delayed; factor 2 = figural or visual memory, short-term and delayed; factor 3 = attention and concentration; factor 4 = visuo spatial orientation, psychomotor processing speed and attention.

Total factor score is the sum of the four independent factor scores; total 6-week factor change is the difference in mean factor score at 6 weeks compared with baseline; smaller total 6-week factor change indicates less improvement from baseline.

ment of neurologic outcome,[44] or a poorly controlled CPB temperature protocol.[45] Furthermore, none of these studies have assessed the full array of neurologic and neurocognitive dysfunction after CPB used in this study.

In the current study, we used a strict temperature, blood gas, and perfusion pressure protocol during CPB (fig. 1). We elected to choose a wide separation in temperature groups (5°C) so that there was a relatively wide difference in temperature management of the two groups during CPB. Our study is the first to report peak and mean CPB temperatures during rewarming in postoperative cognitive outcomes. In addition, we assessed a broad spectrum of short-term postoperative central nervous system dysfunction using precise, previously validated neurologic and neurocognitive test batteries. Neurocognitive testing has been used to assess the onset and severity of dementia,[46] Alzheimer disease,[47,48] and recovery from stroke,[49,50] as well as the efficacy of treatment strategies for Alzheimer disease and early cognitive decline.[51,52] Several important consensus statements have identified key domains for assessment,[53,54] but intervention strategies have varied in their ability to provide substantial protection from decline, similar to the variability of efficacy in stroke trials.[55–57] However, recent studies have demonstrated important associations between neurocognitive function and quality of life after

Table 7. Studies Investigating the Effect of Temperature on Neurologic and Neurocognitive Dysfunction in Patients Undergoing CABG

Authors	Year	Type of Study	No. of Patients	Neurologic Dysfunction	Neurocognitive Dysfunction	Temperature
Grigore *et al.*	2000	Prospective, randomized	300	No relation to temperature	No relation to temperature	28°C, 36°C
Engelman *et al.*[41]	1999	Prospective, randomized	291	No relation to temperature	Not investigated	20°C, 32°C, 37°C
Plourde *et al.*[43]	1997	Prospective, randomized	62	No relation to temperature	No relation to temperature	28°C, 35°C
Mora *et al.*[40]	1996	Prospective, randomized	138	Higher in 35°C group	No relation to temperature	28°C, 35°C
Engelman *et al.*[54]	1996	Prospective, randomized	130	Trend toward a higher incidence in 20°C group	Not investigated	20°C, 32°C, 37°C
Singh *et al.*[44]	1995	Retrospective, nonrandomized	2,585	No relation to temperature	Not investigated	25–30°C, 37°C
Martin *et al.*[39]	1994	Prospective, randomized	1,001	Higher in 35°C group	Not investigated	28°C, 35°C
Warm Heart Investigators[45]	1994	Prospective, randomized	1,732	No relation to temperature	Not investigated	25–30°C, 33–37°C
McLean *et al.*[42]	1994	Prospective, randomized	201	No relation to temperature	No relation to temperature	28°C, 34°C

CABG = coronary artery bypass grafting.

cardiac surgery, emphasizing the relevance of this end point.[58]

In an attempt to adequately assess neurocognitive decline over time while minimizing the potential for neurocognitive testing overlap, we chose to analyze the cognitive function with factor analysis. Factors are, by definition, uncorrelated with each other, and using factor domains as outcomes instead of separate test scores in analyses reduces the concern over redundancy of tests and the possibility of over-representing a single domain of cognitive functioning. Type I errors caused by multiple comparisons are also minimal, and analysis can be conducted on each of the factors as unique outcomes. Incorporating these methodologic improvements, we were unable to detect a beneficial effect of hypothermic CPB on neurocognitive function.

We chose factor analysis because we were faced with the difficulty of assessing eight overlapping cognitive performance scores (table 3) on each individual at each test period. Our goal was to investigate this information as completely as possible while protecting the inferential integrity of our results by avoiding multiple tests of the same thing as much as possible. In a sense, these are "our own" outcome measures; certainly the scores are on a very different scale from the raw scores. However, the factor scores are an exact weighted linear combination of all the original data, and we are confident that, in the absence of accepted scoring rules, this is the least biased way to deal statistically with the multiple correlated scores. The face validity of the factor scores is strongly argued by the fact that validated tests that purport to assess the same cognitive function do, in fact, load on the same cognitive factor. The Randts load together on factor 1, the Figural Memory scores load on factor 2, the Digit Spans load on factor 3, and the Trails B and Digit Symbol, both of which assess attention and visuospatial orientation, load on factor 4. Further validation is provided by the fact that our overall cognitive score (sum of the four factor scores) at baseline correlates very highly with a score calculated as the mean of the z scores from all tests for each individual (Pearson $\rho = 0.969$, Spearman $\rho = 0.972$).

The power to the current project needs some discussion. The cognitive factor scores are standardized in units of 1 SD. This study had at least 80% power at $\alpha = 0.05$ to detect differences in change of less than half an SD on all continuous cognitive outcome measures and differences less than one tenth of an SD on the overall cognitive change score. At a significance level of 0.01, the minimum difference detectable with 80% power for the overall score is 0.105. To determine significance with a difference as small as we observed would have required a total sample size of 288,844. With respect to the less-sensitive categoric outcome, a Fisher exact test with the actual group sizes and a 0.05 two-sided significance level has 80% power to detect the difference between a warm-group proportion of deficit of 39.3% (as observed) and a cold-group proportion of deficit of 21.3%.

Several time points are used for the assessment of neurocognitive dysfunction after cardiac surgery. We chose the 6-week postoperative assessment of neurocognitive function in accord with data previously reported by our institution.[59] There is a substantial reduction in measured neurocognitive deficits between discharge and testing at 4–6 weeks. Some of the markedly reduced cognitive function seen 5 to 7 days after surgery may be influenced by drugs and other factors not related to CPB and surgery. There is little difference between the incidence of cognitive dysfunction measured at the 6-week time point and 6-month or 3-yr follow-up.[59] We have also demonstrated a significant association between 6-week cognitive decline, overall cognitive function, and quality of life at 5 yr.[59] The stability of measured neurocognitive decline at this time point, as well as consideration of retaining patient compliance for follow-up, were the deciding factors in our selection of 6-week neurocognitive follow-up as our primary outcome.

Limitations to the current study include the fact that preoperative neurocognitive tests revealed slightly poorer preoperative performance in the cold group than the warm group. Because cognitive scores decline to a greater degree when starting at a higher level (regression toward the mean), the cold group may have been biased toward a smaller decline in overall cognitive function. However, this limitation was overcome by accounting for the baseline function in the multivariable modeling. A second limitation of our study is related to our assessment of multiple clinical neurologic and neurocognitive outcomes to determine any neuroprotective effect of hypothermic CPB. We realized that by making multiple comparisons we increased the chances of type I error occurrence. Despite this potential limitation, we did not demonstrate any neurologic and neurocognitive differences between treatment groups. A third limitation was that the patients in the cold group, rewarmed at 3–4°C difference between nasopharyngeal and CPB perfusate temperatures, were transiently exposed to central nervous system temperatures greater than 37°C during rewarming, which has been associated with an altered balance of cerebral oxygen supply and demand, leading to jugular venous desaturation and a possible increased risk of cognitive dysfunction.[30,60] Cerebral hyperthermia is also known to worsen the outcome in humans after stroke by increasing the infarct size, morbidity, and mortality.[61,62] Although the occurrence of hyperthermia has not been directly related to neurologic injury after CPB, it is possible that any beneficial effects of hypothermia were counteracted by the mildly hyperthermic period during rewarming.[63] In our analysis, there was no association between the duration and degree of hyperthermic period and cognitive dysfunction. However, we re-

cently found an association of rewarming rate and cognitive function. Slow rewarming rates were associated with less postoperative cognitive decline.[64] Another limitation in the study is that, at 6 weeks, there was significantly lower anxiety and lower depression scores in patients randomized to normothermia.[65] It could be that the lower scores in the warm group might have influenced (increased) the performance of normothermic patients in the current study. This would tend to mask any benefit in the hypothermia group. However, there was no effect of temperature randomization on overall quality of life indicators.[65] Finally, as in any longitudinal study, there were subjects (n = 71) in our study who completed the baseline neuropsychologic testing but were lost at the 6-week follow-up. This loss of follow-up presents serious problems in terms of overall study design. However, the dropout rate was similar in the two treatment groups: 39 of 149 patients (26.2%) in the cold group *versus* 32 of 149 patients (21.5%) in the warm group ($P = 0.415$, Fisher exact test). Overall, the nonreturners scored significantly lower than returners on almost every measure of cognitive function, and our modeling shows that greater decline is associated with cognitive scores that start at a higher level (probably regression toward the mean). If anything, then, our nonreturners, with low initial scores, could be expected also to have low follow-up scores, but with less decline on average than the returners. Thus, it appears that bias caused by loss to follow-up has not invalidated the conclusions because the groups were so similar with respect to 6-week cognitive change, and the percent of dropouts in each group was so similar that any difference attributable to the dropouts would have to be huge to cause a significant effect.

In conclusion, we have demonstrated that a CPB regimen mimicking current practice, including temperatures of 28–30°C and obligate rewarming, does not appear to be neuroprotective. Consideration should be given to future investigation in the areas of other physiological or pharmacologic strategies for neuroprotection during cardiac surgery.

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Appendix 1: Neurologic Outcome Research Group of the Duke Heart Center

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Appendix 2: Cardiothoracic Anesthesia Research Endeavors

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