The impact of temperature in aortic arch surgery patients receiving antegrade cerebral perfusion for >30 minutes: How relevant is it really?

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ABSTRACT

Objective: We examined the early outcomes and the long-term survival associated with different degrees of hypothermia in patients who received antegrade cerebral perfusion (ACP) for >30 minutes.

Methods: During a 10-year period, 544 consecutive patients underwent proximal and total aortic arch surgery and received ACP for >30 minutes and 1 of 3 levels of hypothermia: deep (14.1°C–20°C; n = 116 [21.3%]), low-moderate (20.1°C–23.9°C; n = 262 [48.2%]), and high-moderate (24°C–28°C; n = 166 [30.5%]). A variable called “predicted temperature” was used in propensity-score analysis. Multivariate analysis was done to evaluate the effect of actual temperature on outcomes.

Results: The operative mortality rate was 12.5% (n = 68) overall and was 15.5%, 11.8%, and 11.5% in the deep, low-moderate, and high-moderate hypothermia patients, respectively ($P = .54$). The persistent stroke rate was 6.6% overall and 12.2%, 4.6%, and 6.0% in these 3 groups, respectively ($P = .024$ on univariate analysis). On multivariate analysis, actual temperature was not associated with mortality, but lower temperatures predicted persistent stroke and reoperation for bleeding. In the propensity-matched subgroups, the patients with predicted deep hypothermia had (nonsignificantly) greater rates of persistent stroke (12.2% vs 4.9%; relative risk, 1.08; 95% CI, 0.87–1.15) and reoperation for bleeding (14.6% vs 2.4%; relative risk, 1.14; 95% CI, 0.87–1.15) than the patients with predicted moderate hypothermia. On long-term follow-up (mean duration, 5.12 years), 4- and 8-year survival rates were 62.3% and 55.7% in the deep hypothermia group and 75.4% and 74.2% in the moderate hypothermia group ($P = .0015$).

Conclusions: In proximal and arch operations involving ACP for >30 minutes, greater actual temperatures were associated with less stroke and reoperation for bleeding. There were no significant differences among the predicted hypothermia levels, although a trend toward a higher rate of adverse events was noticed in the deep hypothermia group. Long-term survival was better in the moderate hypothermia group. (J Thorac Cardiovasc Surg 2017;153:767–76)

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In arch surgery with >30 minutes antegrade cerebral perfusion, lower actual temperature correlated with more stroke.

Central Message

Among patients who received >30 minutes of antegrade cerebral perfusion, greater actual temperatures were associated with fewer adverse events. A similar, nonsignificant trend was seen with the predicted hypothermia levels.

Perspective

In arch operations involving circulatory arrest, moderate hypothermia is increasingly used with selective antegrade cerebral perfusion. Among patients who received >30 minutes of antegrade cerebral perfusion, greater actual temperatures were associated with fewer adverse events. A similar, nonsignificant trend was seen with the predicted hypothermia levels. Long-term mortality was lower in the moderate hypothermia group, warranting more investigation.

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As the traditional perfusion strategy for brain protection during aortic arch surgery,^{1,2} deep hypothermic circulatory arrest (DHCA) has been used successfully by

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Abbreviations and Acronyms

ACP	= antegrade cerebral perfusion
CABG	= coronary artery bypass grafting
CI	= confidence interval
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
ECMO	= extracorporeal membrane oxygenation
ET	= elephant trunk
MOF	= multiorgan failure
NIRS	= near-infrared spectroscopy

respected surgical groups.³ One of the mechanisms of brain protection during hypothermia is cerebral metabolic suppression with a decreased oxygen demand.⁴ At 15°C, the duration of safe circulatory arrest is <29 minutes,⁴ even though “safe periods” have been reported of up to 40 minutes at deep hypothermic temperatures.⁵ In addition, faster recovery from tissue acidosis is achieved with hypothermic ischemia.⁶

According to a recent consensus statement issued by thoracic aortic surgeons, the different levels of hypothermia in aortic surgery are classified as profound ($\leq 14^\circ\text{C}$), deep (14.1°C – 20.0°C), moderate (20.1°C – 28.0°C), and mild (28.1°C – 34.0°C).⁷ In most proximal arch procedures, the open distal anastomosis can be accomplished in <30 minutes. For most complex repairs, however, additional time is required. With adjunctive antegrade cerebral perfusion (ACP) for brain protection, moderate hypothermia is considered a safe option.^{8–12} In the present study, we evaluated the effect of temperature and different degrees of hypothermia (14.1°C – 28°C) in patients receiving ACP for >30 minutes, and we examined short-term outcomes and long-term survival.

PATIENTS AND METHODS

Patients

From January 2005 to August 2015, 544 consecutive patients underwent proximal and/or total arch surgery and received ACP for >30 minutes at our hospital. Patients who did not receive ACP or whose ACP duration was ≤ 30 minutes were excluded from the study. The data were obtained from a prospectively maintained database, and the study was approved by the institutional review board of Baylor College of Medicine. Follow-up information was obtained from the Social Security Death Master Index, clinic visits, information from the referring physician's office, and telephone calls with patients or their families. If we were unable to find evidence of death through any of these sources, then we assumed that the patient was alive.

We categorized the patients according to duration of ACP and hypothermia level. The ACP time was 31 to 45 minutes in 238 patients (43.8%) and >45 minutes in 306 patients (56.3%). The procedures were performed with circulatory arrest and 3 levels of hypothermia: 14.1°C to 20°C (deep hypothermia: $n = 116$ [21.3%], mean temperature $17.1^\circ\text{C} \pm 1.5^\circ\text{C}$), 20.1°C to 23.9°C (low-moderate hypothermia: $n = 262$ [48.2%], mean temperature

$22.6^\circ\text{C} \pm 1.0^\circ\text{C}$), and 24°C to 28°C (high-moderate hypothermia: $n = 166$ [30.5%], mean temperature $24.5^\circ\text{C} \pm 0.8^\circ\text{C}$). We chose these hypothermia levels to be in agreement with the categories used in an expert consensus statement on hypothermia in aortic arch surgery.⁷

Moderate hypothermia was divided into 2 ranges (high-moderate and low-moderate) because moderate hypothermia involved a wide range of temperatures and because of our current preference for warmer temperatures. Bilateral ACP was administered to 370 patients (68%), and unilateral ACP was used in the other 174 patients (32%). When we anticipated that the repair would be more complex, we used lower temperatures and bilateral ACP, although very early in the study period we relied more on low temperatures for brain protection. Bilateral ACP was also used when a change of more than 10% was noted on near-infrared spectroscopy (NIRS). Lately, bilateral ACP has been our default approach because it is quick and easy and does not add time to the operation. Intraoperatively, the temperature was measured nasopharyngeally. The cerebral perfusate temperature and core body nasopharyngeal temperature were similar (the perfusate temperature may have been 1°C lower).

To eliminate the effect of physician bias with regard to how low we wanted the temperature to be, we created a new variable called “predicted temperature,” which is a balancing score temperature based on each patient's actual hypothermic temperature and on preoperative and intraoperative variables. When grouped by predicted temperature, there were 124 (22.8%) patients in the deep hypothermia group, 330 (60.8%) in the low-moderate group, and 89 (16.4%) in the high-moderate group.

The lowest nasopharyngeal temperature was also recorded, which was 14.3°C for the entire group. Table 1 shows patient characteristics and demographic variables. The ACP time was defined as the period during circulatory arrest in which the patient was receiving ACP. The circulatory arrest time was the total period of circulatory arrest with and without ACP; circulatory arrest was initiated when the desired nasopharyngeal temperature was achieved. The cardiopulmonary bypass (CPB) time was the period of CPB, not including the ACP time or the circulatory arrest time. Finally, the myocardial ischemia time was the time from crossclamp placement until clamp removal or from the initiation of circulatory arrest until clamp removal. The outcomes have been defined previously.¹³

Procedure

In all procedures, NIRS was used to measure intraoperative regional cerebral oxygen saturation. The nasopharyngeal temperature was recorded when circulatory arrest was initiated. Unilateral ACP was delivered via a graft sutured into the innominate or right axillary artery to establish arterial inflow when CPB was initiated. If the right axillary artery or the innominate artery was not used, a 9-French Pruitt balloon-tip catheter (LeMaitre Vascular, Inc, Burlington, Mass) was used to deliver unilateral ACP via the left common carotid artery. For bilateral ACP, when the right axillary or the innominate artery was used for cannulation, the same catheter delivered ACP to the left cerebral hemisphere via the left common carotid artery. The target flow of 10 to 15 mL/kg/min was adjusted according to the NIRS signal. The pressure was measured via the right and/or left radial arterial line and was maintained at around 50 to 70 mm Hg. Intraoperative details have previously been described.^{13,14} Table 2 shows the procedural details.

Statistical Analysis

Differences in the distribution of preoperative characteristics, operative variables, and outcomes among the deep, low-moderate, and high-moderate hypothermia groups were tested by the use of χ^2 analysis or the Fisher exact test when necessary, for the categorical variables, and the nonparametric Kruskal-Wallis test for the continuous variables. Stepwise logistic multivariate analyses were performed to identify predictors for the adverse outcomes of interest by analyzing the following 30 preoperative and operative variables: temperature at which circulatory arrest was

TABLE 1. Preoperative characteristics of total (based on actual temperature) and propensity-matched (based on predicted temperature) cohorts

Characteristic	Total cohort					Propensity-matched cohort			
	All patients (n = 544)	Deep (n = 116)	Low- moderate (n = 262)	High- moderate (n = 166)	P value	All patients (n = 82)	Deep (n = 41)	Moderate (n = 41)	Std diff
Age, y	64 (52-71.5)	66 (51-71.5)	64 (53-71)	64 (52-72)	.94	59.5 (48-72)	65 (50-72)	56 (45-71)	0.28
Male sex	350 (64.3)	70 (60.3)	172 (65.7)	108 (65.1)	.59	55 (67.1)	24 (58.5)	31 (75.6)	-0.37
Urgency of operation					.56				0.21
Elective	354 (65.1)	72 (62.1)	169 (64.5)	53 (68.1)		54 (65.9)	25 (61.0)	29 (70.7)	
Emergent/urgent	190 (34.9)	44 (37.9)	93 (35.5)	53 (31.9)		28 (34.2)	16 (39.0)	12 (29.3)	
Smoking	254 (46.7)	58 (50.0)	127 (48.5)	69 (41.6)	.27	42 (51.2)	22 (53.7)	20 (48.8)	0.10
Redo sternotomy	233 (42.8)	49 (42.2)	113 (43.1)	71 (42.8)	.99	39 (47.6)	20 (48.8)	19 (46.3)	0.05
Hypertension	464 (85.3)	92 (79.3)	223 (85.1)	149 (89.8)	.051	69 (84.2)	35 (85.4)	34 (82.9)	0.07
Chronic obstructive pulmonary disease	183 (33.6)	40 (34.5)	86 (32.8)	57 (34.3)	.93	27 (32.9)	15 (29.3)	12 (29.3)	0.16
Preoperative coronary event*	201 (37.0)	42 (36.2)	94 (35.9)	65 (39.2)	.78	29 (35.4)	16 (39.0)	13 (31.7)	0.15
Acute/subacute aortic dissection	127 (23.4)	28 (24.1)	66 (25.2)	33 (19.9)	.44	21 (25.6)	12 (29.3)	9 (22.0)	0.17
Congestive heart failure	219 (40.3)	59 (50.9)	104 (39.7)	56 (33.7)	.015	26 (31.7)	13 (31.7)	13 (31.7)	0.00
Renal dysfunction	104 (19.1)	19 (16.4)	55 (21.0)	30 (18.1)	.53	17 (20.7)	7 (17.1)	10 (24.4)	-0.18
History of stroke/TIA	76 (14.0)	20 (17.2)	34 (13.0)	22 (13.3)	.52	10 (12.2)	5 (12.2)	5 (12.2)	0.00
Diabetes	49 (9.0)	7 (6.0)	25 (9.5)	17 (10.2)	.44	3 (3.7)	2 (4.9)	1 (2.4)	0.13
Previous proximal aortic surgery	213 (39.2)	47 (40.5)	103 (39.3)	63 (38.0)	.91	36 (43.9)	18 (43.9)	18 (43.9)	0.00
Previous CABG surgery	46 (8.5)	10 (8.6)	21 (8.0)	15 (9.0)	.93	10 (12.2)	4 (9.8)	6 (14.6)	-0.15

Data are reported as median (25%-75% IQR) for continuous variables and number (percentage) for categorical variables. *Std diff*, Standardized difference; *TIA*, transient ischemic attack; *CABG*, coronary artery bypass grafting. *Preoperative myocardial infarction, CABG, percutaneous transluminal coronary angioplasty stent, coronary artery disease, and pacemaker.

initiated, year of surgery, concomitant coronary artery bypass grafting (CABG), concomitant aortic root replacement, type of cannulation, age, sex, surgical priority, smoking status, hypertension, chronic obstructive pulmonary disease, preoperative coronary events, congestive heart failure, renal disease, preoperative neurologic deficit, diabetes mellitus, CPB time, ischemia time, ACP time, redo sternotomy, acute/subacute aortic dissection, packed red blood cell transfusion, bilateral ACP infusion, total arch replacement, previous aortic root replacement, previous ascending aortic surgery, previous ascending and hemiarch surgery, previous ascending and arch surgery, previous CABG, and previous aortic valve replacement.

For those outcomes that were associated with the temperature at which circulatory arrest was initiated, we ran the models a second time to see whether categorical (vs continuous) temperature was a predictor. In addition, predicted temperature was derived by modeling the actual temperature as the dependent variable and the following factors as independent variables: year of surgery, priority of surgery, acute type I aortic dissection, age, male sex, smoking, redo sternotomy, hypertension, chronic obstructive pulmonary disease, preoperative coronary event, congestive heart failure, preoperative renal disease, preoperative neurologic deficit, diabetes, total arch replacement, concomitant aortic root replacement, concomitant CABG, packed red blood cell transfusion, bilateral ACP, previous aortic root replacement, previous ascending aortic replacement, previous ascending and hemiarch replacement, previous ascending and arch replacement, previous aortic valve replacement, CPB time, ischemia time, and ACP time.

Multicollinearity was checked with regression analysis. To reduce the effects of any potential bias between the deep and moderate hypothermia groups, we matched the patients by means of propensity score, which was calculated for each patient by the use of multivariate logistic regression. In the model, deep versus moderate hypothermia (low- and high-moderate were grouped together for simplicity and because of the smaller number of patients in this analysis) was used as the

dependent variable; the variables used in the aforementioned multivariate regression models were included as covariates. We then used a greedy matching algorithm without replacement to match each patient in the deep hypothermia group to a patient in the moderate hypothermia group with a similar propensity score, resulting in a matched cohort of 82 patients. We compared these 2 groups' preoperative and intraoperative patient characteristics by the use of standardized differences. The adverse outcomes were compared by calculating the relative risk with a 95% confidence interval (95% CI).

We then used Kaplan-Meier analysis to estimate the survival functions for the deep and moderate hypothermia groups in the overall cohort. The survival curves were compared by use of the log-rank test. Time to death from the date of surgery was computed for patients who died before March 31, 2016 (the end date of the study). Those who did not die before the end of the study were considered as censored. Statistical analyses were performed with SAS version 9.1 (SAS Software, Inc, Cary, NC), and $P < .05$ was considered the cutoff for significance.

RESULTS

Operative Mortality

The overall operative mortality rate was 12.5% ($n = 68$) (Table 3), including 18 patients (15.5%) who underwent deep hypothermia. Nine of these 18 nonsurvivors had acute type I aortic dissection (5 had presented in extremis, and 1 patient died intraoperatively). Five other nonsurvivors underwent total arch replacement (redo or primary) and were placed on extracorporeal membrane oxygenation (ECMO) because of difficulty being weaned from CPB. Postoperatively, these 5 patients could not be weaned

TABLE 2. Intraoperative variables for total (based on actual temperature) and propensity-matched (based on predicted temperature) cohorts

Variable	Total cohort				P value	Propensity-matched cohort			
	All patients (n = 544)	Deep (n = 116)	Low-moderate (n = 262)	High-moderate (n = 166)		All patients (n = 82)	Deep (n = 41)	Moderate (n = 41)	Std diff
Procedure									
Ascending and hemiarch	236 (43.3)	45 (38.8)	113 (42.9)	78 (47.0)	.46	45 (54.9)	21 (51.2)	24 (58.5)	−0.15
Ascending only	3 (0.6)	1 (0.9)	2 (0.8)	0 (0.0)	.89	2 (2.4)	2 (4.9)	0 (0.0)	0.32
TAR	305 (56.2)	70 (60.3)	147 (56.3)	88 (53.0)	.47	36 (43.9)	18 (43.9)	18 (43.9)	0.00
Concomitant procedures									
Aortic root replacement	87 (16.0)	14 (12.1)	46 (17.6)	27 (16.3)	.40	16 (19.5)	5 (12.2)	11 (26.8)	−0.38
Aortic valve	175 (32.2)	32 (27.6)	89 (34.0)	54 (32.5)	.47	25 (30.5)	12 (29.3)	13 (31.7)	−0.05
Coronary artery bypass grafting	61 (11.2)	16 (13.8)	26 (9.9)	19 (11.5)	.54	11 (13.4)	4 (9.8)	7 (17.1)	−0.22
Tricuspid, mitral, PFO repair	15 (2.8)	5 (4.3)	6 (2.3)	4 (2.4)	.54	2 (2.4)	2 (0.9)	0 (0.0)	0.32
ACP type					<.0001				0.00
Unilateral	174 (32.0)	96 (82.8)	46 (17.6)	32 (19.3)		78 (95.1)	39 (95.1)	39 (95.1)	
Bilateral	370 (68.0)	20 (17.2)	216 (82.4)	134 (80.7)		4 (4.9)	2 (4.9)	2 (4.9)	
PRBC	426 (78.3)	103 (88.8)	199 (76.0)	124 (74.7)	.0081	67 (81.7)	34 (82.9)	33 (80.5)	0.06
ACP >45 min	306 (56.3)	47 (40.5)	167 (63.7)	92 (55.4)	.0001	30 (36.6)	14 (34.2)	16 (39.0)	0.10
Operative times, min									
CPB time	137 (101-183)	137.5 (107-178)	141 (98-189)	133 (104-172)	.68	132 (111-173)	137 (107-171)	130 (113-173)	0.03
Myocardial ischemia time	94 (73-126)	89 (69-121)	97 (74-132)	94 (75-122)	.14	91 (69-117)	81 (63-110)	95 (79-118)	−0.20
ACP time	49 (37-66.5)	42 (36-57)	54 (40-71)	48.5 (37-66)	.0004	38.5 (34-50)	38 (33-49)	40 (35-50)	0.16
Circulatory arrest time	51 (39-69)	45 (38-63)	55 (41-72)	49.5 (37-66)	.0096	41.5 (35-52)	42 (34-53)	41 (36-51)	0.17

Data are reported as median (25%-75% IQR) for continuous variables and number (percentage) for categorical variables. *Std diff*, Standardized difference; *TAR*, total arch replacement; *PFO*, patent foramen ovale; *ACP*, antegrade cerebral perfusion; *PRBC*, packed red blood cells; *CPB*, cardiopulmonary bypass.

from ECMO, and support was withdrawn at the family's request. Three other patients developed multiorgan failure (MOF) after redo total arch replacement (n = 2) and infective root endocarditis (n = 1). The remaining patient underwent urgent repair of a symptomatic total arch aneurysm; postoperatively, that patient had a ruptured extent I thoracoabdominal aneurysm, underwent emergent

replacement of the thoracoabdominal aorta, and had a fatal stroke.

Of the patients who underwent low-moderate hypothermia, 31 (11.8%) died, including 12 who had acute type I aortic dissection. Of these 12 nonsurvivors, 4 presented in extremis (of whom 1 died intraoperatively), 4 others died of MOF, 2 had fatal strokes, 1 developed a diffuse

TABLE 3. Postoperative outcomes for the total cohort (n = 544) according to actual temperature

Outcome	All patients (n = 544)	Deep (n = 116)	Low-moderate (n = 262)	High-moderate (n = 166)	P value
Operative mortality	68 (12.5)	18 (15.5)	31 (11.8)	19 (11.5)	.54
30-d mortality	62 (11.4)	16 (13.8)	28 (10.7)	18 (10.8)	.66
Stroke	50 (9.2)	17 (14.8)	20 (7.7)	13 (7.8)	.071
Persistent stroke	36 (6.6)	14 (12.2)	12 (4.6)	10 (6.0)	.024
Renal failure	113 (20.9)	29 (25.2)	46 (17.6)	38 (22.9)	.19
Persistent renal failure	29 (5.4)	8 (7.0)	14 (5.4)	7 (4.2)	.62
Persistent paraplegia/paraparesis	4 (0.7)	0 (0.0)	2 (0.8)	2 (1.2)	.68
Total neurologic events	73 (13.5)	21 (18.3)	33 (12.6)	19 (11.5)	.23
Persistent total neurologic events	39 (7.2)	14 (12.2)	14 (5.4)	11 (6.6)	.062
Reoperation for bleeding	61 (11.3)	24 (20.9)	20 (7.7)	17 (10.2)	.0009
Ventilation >48 h	235 (43.4)	60 (52.2)	117 (44.8)	58 (34.9)	.016
Tracheostomy	94 (17.3)	26 (22.6)	47 (18.0)	21 (12.7)	.095
Pericardial window	17 (3.1)	7 (6.1)	8 (3.1)	2 (1.2)	.072

Data are reported as median (25%-75% IQR) for continuous variables and number (percentage) for categorical variables.

TABLE 4. Postoperative outcomes for the propensity-matched cohort based on predicted temperature

Outcome	All patients (n = 82)	Deep (n = 41)	Moderate (n = 41)	RR (95% CI)
Operative mortality	8 (9.8)	4 (9.8)	4 (9.8)	1 (0.86-1.16)
30-d mortality	7 (8.5)	3 (7.3)	4 (9.8)	0.97 (0.87-1.15)
Stroke	8 (9.8)	6 (14.6)	2 (4.9)	1.11 (0.86-1.16)
Persistent stroke	7 (8.5)	5 (12.2)	2 (4.9)	1.08 (0.87-1.15)
Renal failure	13 (15.9)	11 (26.8)	2 (4.9)	1.3 (0.81-1.23)
Persistent renal failure	3 (3.7)	2 (4.9)	1 (2.4)	1.03 (0.92-1.09)
Total neurologic events	9 (11.0)	6 (14.6)	3 (7.3)	1.09 (0.85-1.17)
Persistent total neurologic events	7 (8.5)	5 (12.2)	2 (4.9)	1.08 (0.87-1.15)
Reoperation for bleeding	7 (8.5)	6 (14.6)	1 (2.4)	1.14 (0.87-1.15)
Ventilation >48 h	32 (39.0)	19 (46.3)	13 (31.7)	1.27 (0.68-1.47)
Tracheostomy	11 (13.4)	7 (17.1)	4 (9.8)	1.09 (0.85-1.18)
Pericardial window	6 (7.3)	3 (7.3)	3 (7.3)	1 (0.88-1.13)

Data are reported as median (25%-75% IQR) for continuous variables and number (percentage) for categorical variables. RR, Relative risk; CI, confidence interval.

coagulopathy postoperatively, and 1 experienced sudden syncope during the recovery period and developed an anoxic brain injury. Eight nonsurvivors developed MOF (5 of these had a total arch replacement). Six other patients were placed on ECMO because of inability to be weaned from CPB; postoperatively, patients remained in heart failure and could not be weaned from ECMO, and the family consented to withdrawal of life support. Three patients had a cardiac arrest postoperatively in the intensive care unit and died despite cardiopulmonary resuscitation, and 2 other patients had a fatal stroke after a redo arch procedure.

Of the patients who underwent proximal and arch procedures with high-moderate hypothermia, 19 (11.5%) died. Seven of these patients developed MOF (4 after redo arch procedures, 1 after a redo homograft root operation, 1 after repair of a type I aortic dissection, and 1 after proximal arch surgery). Four other nonsurvivors had a cardiac arrest postoperatively and died despite cardiopulmonary resuscitation. Four additional patients could not be weaned from ECMO (3 of these had redo proximal arch and root operations), and 3 patients had a fatal stroke (2 after redo arch operations and 1 after repair of acute type I aortic dissection). After undergoing arch replacement, another patient developed a symptomatic thoracoabdominal aortic aneurysm and required urgent thoracoabdominal aortic replacement; he subsequently developed MOF and died.

In the multivariate analysis, the temperature and the 3 different hypothermia levels (14.1°C-20°C, 20.1°C-23.9°C, and 24°C-28°C) did not appear to affect mortality, even though lower actual temperatures were (nonsignificantly) associated with greater mortality. Operative mortality was associated with congestive heart failure and prolonged CPB. The propensity-matching analysis (n = 82) based on predicted temperatures showed the

same results for the deep hypothermia group versus the moderate hypothermia group (Table 4). In a subgroup analysis involving only the patients with prolonged ACP (>45 minutes), the mortality in the deep hypothermia group was 17%, versus 12% for the moderate group, and this difference was not significant ($P = .34$). In addition, the mortality rate was not different for patients who had an ACP time of 31 to 45 minutes versus >45 minutes within the same range of hypothermia (deep [$P = .71$] or moderate [$P = .82$]).

Neurologic Events

In the overall cohort, 36 (6.6%) of the 542 patients had a persistent stroke (2 of whom died intraoperatively) (Table 3). These patients included 14 (12.2%) in the deep hypothermia group, 12 (4.6%) in the low-moderate hypothermia group, and 10 (6.0%) in the high-moderate hypothermia group ($P = .024$) (Table 3). The same trend toward greater rates of total neurologic events, strokes, and persistent strokes was noted among the deep hypothermia (per predicted temperature) patients in the propensity-score matching analysis, although this trend was not statistically significant. In the multivariate analysis, the 3 different hypothermia levels (per actual temperature) did not appear to affect neurologic outcomes, but when actual temperature was used as a continuous variable, we noticed a significant association between lower temperature and greater rates of stroke and persistent stroke (Table 5). In a subgroup analysis of patients with a shorter (31-45 minutes) versus a longer ACP time (>45 minutes) within the same hypothermia range, the incidence of stroke did not differ (deep hypothermia: 13% vs 17% [$P = .55$]; moderate hypothermia: 8.9% vs 7% [$P = .47$]). When we analyzed only the patients with an ACP time

TABLE 5. Multivariate results for factors associated with adverse outcomes

Outcome	Variables in multivariate analysis	P value	OR (95% CI)
Operative mortality	Smoker	.0075	2.22 (1.24-3.98)
	CHF	<.0001	4.46 (2.44-8.17)
	CPB time	<.0001	1.01 (1.01-1.01)
Stroke C = 0.66, HL <i>P</i> = .51	Temperature*	.018	0.90 (0.82-0.98)
	Priority†	.0012	2.66 (1.47-4.82)
Persistent stroke C = 0.68, HL <i>P</i> = .66	Temperature*	.020	0.88 (0.79-0.98)
	Preoperative neurologic deficit	.018	2.62 (1.18-5.84)
	Acute	.0039	2.85 (1.40-5.80)
Renal failure C = 0.72, HL <i>P</i> = .10	Age	.021	1.02 (1.00-1.04)
	Preoperative coronary event	.044	1.60 (1.01-2.52)
	CHF	.046	1.58 (1.01-2.49)
	Preoperative renal	.016	1.90 (1.13-3.19)
	CPB time	<.0001	1.01 (1.00-1.01)
	PRBC	.029	2.15 (1.08-4.28)
Total neurologic events C = 0.69, HL <i>P</i> = .87	Concomitant CABG	.044	2.10 (1.02-4.31)
	Acute	<.0001	4.05 (2.36-6.94)
	PRBC	.018	2.47 (1.17-5.24)
Persistent total neurologic events C = 0.67, HL <i>P</i> = .95	Preoperative neurologic deficit	.0025	3.17 (1.50-6.71)
	Acute	.0068	2.63 (1.31-5.29)
	Previous CABG	.038	2.63 (1.05-6.57)
Reoperation for bleeding C = 0.69, HL <i>P</i> = .34	Temperature*	.0005	0.86 (0.79-0.94)
	CPB time	<.0001	1.01 (1.00-1.01)

OR, Odds ratio; CI, confidence interval; HL, Hosmer-Lemeshow; CHF, congestive heart failure; CPB, cardiopulmonary bypass; PRBC, packed red blood cells; CABG, coronary artery bypass grafting. *Temperature was analyzed as a continuous variable. Greater temperatures were associated with lower incidences of this outcome. †Priority: elective versus emergent/urgent.

>45 minutes, however, the overall observed stroke rate in the deep hypothermia group (17%) was more than double that in the moderate hypothermia group (7%) (*P* = .041).

Among the 542 operative survivors, 4 patients (0.7%) had a persistent spinal cord injury: either paraplegia (1 each in the low-moderate and high-moderate groups) or paraparesis (also 1 each in the low-moderate and high-moderate groups). No spinal cord injury was observed in

VIDEO 1. Total arch stage I elephant trunk under moderate hypothermia (24°C), followed by aortic valve replacement. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31684-1/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31684-1/addons).

the deep hypothermia group. Three of the 4 patients with spinal cord injuries underwent total arch replacement with an elephant trunk (ET) (*n* = 1 frozen; *n* = 2 traditional) (Video 1), and the fourth patient had total arch replacement without an ET. In that patient, a cerebrospinal fluid drain was inserted postoperatively, and the patient recovered with residual weakness. Because the frozen-ET recipient with paraplegia had multiple previous spine operations, a cerebrospinal fluid drain could not be inserted. The other paraplegia patient had a concomitant ischemic stroke and died. Other adverse outcomes are listed in Table 3.

Long-Term Survival

The 2-, 4-, and 8-year survival rates were 70.4%, 62.3%, and 55.7% in the deep hypothermia group versus 78.5%, 75.4%, and 74.2% in the moderate hypothermia group (*P* = .0015). The mean follow-up period was 5.12 years (95% CI, 4.68-5.67 years). The Kaplan-Meier survival curves based on the 2 temperature levels for the entire cohort are shown in Figure 1.

DISCUSSION

According to the Yale thoracic aortic surgery group, the use of straight DHCA results in the preservation of neurocognitive function and excellent clinical outcomes.¹⁵ We have reported that the “safe stroke” period of circulatory arrest is limited to approximately 40 minutes.⁵ Despite the obvious advantages of a bloodless surgical field and not having multiple cannulas in that field during straight DHCA, there is a trend toward

Time Since Surgery	2 y	4 y	6 y	8 y	10 y
Deep Hypothermia					
Number at risk	80	68	59	53	16
Survival % (95% CI)	70.4 (62.0-78.8)	62.3 (53.3-71.3)	56.8 (47.6-66.0)	55.7 (46.5-64.9)	55.7 (46.5-64.9)
Moderate Hypothermia					
Number at risk	263	168	95	21	-
Survival % (95% CI)	78.5 (74.6-82.4)	75.4 (71.1-79.7)	74.2 (69.7-78.7)	74.2 (69.7-78.7)	-

Log-rank p-value=0.0015. Hazard ratio=0.58 (95% CI 0.41-0.81)

FIGURE 1. Kaplan-Meier survival curves for the entire cohort. The median follow-up time is 5.12 years (95% CI 4.68-5.67). 95% CI, 95% Confidence interval.

the use of moderate hypothermia with adjunctive ACP,¹⁶ which potentially can provide better neuroprotection¹⁷ and decrease the early mortality rate.¹² However, the technical details of ACP with regard to cannulation site, unilateral versus bilateral use, and the perfusate temperature of ACP versus the core temperature during selective ACP with systemic circulatory arrest are still debated.¹⁸⁻²¹

In this study, we analyzed the effects of temperature and of different levels of hypothermia (deep: 14.1°C-20°C; low-moderate: 20.1°C-23.9°C; and high-moderate: 24°C-28°C) in patients who underwent complex aortic arch surgery requiring ACP for >30 minutes. The temperature of the cerebral perfusate was very similar to the core temperature (nasopharyngeal), with maybe 1°C or less difference, and the

different temperature levels were based on the temperature at which circulatory arrest was initiated. On multivariate analysis, the different hypothermia levels did not appear to play a role in mortality, even though mortality was greater (although not significantly so) in patients with lower hypothermic temperatures. Mortality was associated with CPB time, New York Heart Association functional class III or IV status, and current or previous smoking.

Other researchers, as well as our own group, have suggested that a prolonged CPB time is associated with mortality.^{12,22-24} In our previous study,¹² which included all patients who received ACP regardless of the ACP time and data from only a 3-year period, deep hypothermia was associated independently with in-hospital mortality; this association was not seen in the present study, although

a trend toward greater mortality was noted. In a subgroup analysis of our data in which we examined only the patients with prolonged ACP (>45 minutes) and compared the deep and the moderate hypothermia groups, the mortality rate was nonsignificantly greater in the deep hypothermia group ($P = .34$). In addition, the mortality rate was not different for patients who had an ACP time of 31 to 45 minutes versus >45 minutes within the same range of hypothermia.

In comparing the 3 levels of hypothermia with regard to neurologic events, we found that the incidence of persistent stroke was greater in the deep hypothermia group versus the moderate hypothermia groups on univariate analysis (Table 3). In the propensity-matching analysis based on the predicted temperatures, a nonsignificant association was noted between higher stroke rate and lower predicted temperature (Table 4). Although in the multivariate analysis the 3 levels of hypothermia (per actual temperature) were not associated with significant differences in stroke rate, there appeared to be an independent association between lower actual temperature and higher incidence of stroke. This finding agrees with the greater rate of neurologic events in the lower-temperature groups in our previous study.¹² In addition, our multivariate analysis showed that prior neurologic event and acute type I aortic dissection were associated with persistent stroke and that emergent status was associated with overall stroke. Other investigators have shown that urgent operative status, acute type I aortic dissection, and a history of neurologic events were predictors of stroke.^{22,25,26} In addition, the incidence of stroke did not differ between patients with a shorter versus a longer ACP time (>45 minutes) within the same hypothermia range (deep hypothermia: 13% vs 17% [$P = .55$]; moderate hypothermia: 8.9% vs 7% [$P = .47$]). However, in the patients with an ACP time of >45 minutes, the overall observed stroke rate in the deep hypothermia group (17%) was more than double that in the moderate hypothermia group (7%) ($P = .041$), suggesting that complex arch reconstructions requiring prolonged ACP can be performed safely with the use of moderate hypothermia.

These findings imply that the “benefits” of deep hypothermia must be reexamined, given the potential negative effects of this technique.²⁷ An elevated incidence of temporary neurologic events and fine motor deficits was observed by Reich and colleagues²⁸ in cases involving DHCA of >25 minutes, and persistent or temporary neurologic events may be encountered even more frequently in cases of DHCA lasting for >40 minutes.⁵ In studying 305 thoracic aortic operations involving ACP, Pacini and associates²⁴ compared 2 groups of

patients: those undergoing moderate systemic hypothermia ($\geq 25^{\circ}\text{C}$) (189 patients with ACP times of 63 ± 37.7 minutes) and deeper hypothermia ($< 25^{\circ}\text{C}$) (116 patients with ACP times of 58.6 ± 35.6 minutes). In that study, no differences were observed between the 2 groups, and ACP time and temperature were not associated with temporary or persistent neurologic events. In our study, even though the different levels of hypothermia were not associated with temporary or persistent neurologic events, lower temperature was associated significantly with greater risk of persistent stroke. In the study by Pacini and colleagues,²⁴ prolonged CBP time was associated with persistent neurologic deficits, but we did not observe this association in our patients.

In a study of 347 patients who underwent aortic operations (excluding urgent or emergent cases), Urbanski and colleagues²⁹ found that the duration of circulatory arrest was 18 ± 11 minutes (range, 6-70 minutes) and the lowest rectal temperature was $31.5^{\circ}\text{C} \pm 1.6^{\circ}\text{C}$ (range, 26.0°C - 35.0°C) for the overall group; these 2 variables were 34 ± 12 minutes (range, 17-70 minutes) and $29.9^{\circ}\text{C} \pm 1.7^{\circ}\text{C}$ (range, 26.0°C - 34.6°C), respectively, for 77 patients who had total/subtotal arch replacement. The incidence of neurologic complications was remarkably low, and the authors suggested that mild-to-moderate hypothermia with cerebral perfusion is a safe method in aortic arch surgery.

We did not use mild hypothermia in our study, but we agree that moderate hypothermia with ACP is a safe technique for performing proximal aortic surgery, and our results partially support that statement, even though the current study is focused only on patients who received ACP for more than 30 minutes. The persistent stroke rate was greater in our moderate hypothermia group than in Urbanski and coworkers' patients, but our series included all consecutive patients, elective and emergent cases, and type I aortic dissection procedures.

With greater temperatures, spinal cord ischemia is a concern. Strauch and colleagues³⁰ at Mount Sinai Hospital showed in pigs that moderate hypothermia during hypothermic circulatory arrest can protect the spinal cord for a prolonged period. Our group had 4 patients (0.7%) with spinal cord injury (2 with paralysis and 2 with paraparesis). All of them had moderate hypothermia (2 in the low range and 2 in the high range). In 3 of these 4 patients, the ACP time was >45 minutes; all 3 patients had ET operations, including 1 frozen ET procedure. Given the multifactorial nature of spinal cord ischemia, it is unclear what caused the spinal cord event: the ET procedure itself, the prolonged ACP time, the greater temperature, or a combination of all 3 factors. Although the precise cause

may be difficult to determine and the numbers are too small for any conclusions to be drawn, perhaps a lower temperature should be considered when an ET or frozen ET procedure is contemplated. Kamiya and colleagues¹¹ found an increased incidence of spinal cord ischemia in patients who had prolonged circulatory arrest with ACP times of >60 minutes and moderate hypothermia (25°C-28°C); no paraplegia was observed in the group that had lower temperatures (20°C-24°C) during the proximal procedures.

Our overall rate of postoperative renal injury was 20.9% according to actual temperature and 15.9% according to predicted temperature, which agrees with results reported by others.³¹ Despite a greater incidence of this complication in the deep hypothermia group, there were no significant differences among the hypothermia level groups (based on actual and predicted temperature). For postoperative renal injury, CPB time and increasing age were independent predictors (as others have also shown¹¹), and so was preoperative renal status.³¹ No ischemic damage to the viscera was noted in our study, maybe because the ischemic tolerance of the viscera exceeds that of the spinal cord; liver function test data were not recorded.

More coagulation disturbances have been observed at lower temperatures.²⁷ In our study, more packed red blood cell transfusions were necessary in the deep hypothermia group ($P = .0081$). Although scientific evidence is inadequate, our multivariate analysis showed that in patients with ACP times of >30 minutes, the rate of reoperation for bleeding was significantly higher in the lower-temperature patients. In the propensity-matching analysis for predicted temperature, the patients who underwent deep (vs moderate) hypothermia had nonsignificantly greater rates of return to the operating room to correct bleeding events (14.6% vs 2.4%; relative risk, 1.14; 95% CI, 0.87-1.15). A greater rate of bleeding also has been observed by others.¹¹ In our series, prolonged CPB time also independently predicted reoperation for bleeding; this was to be expected, because prolonged CPB can signify a more complex and prolonged operation.

In the entire cohort, long-term survival was significantly better in patients who underwent aortic arch surgery under moderate hypothermia. This was an interesting finding that may require further evaluation by us, as well as others.

Limitations of our study include its retrospective design, with its inherent bias. In addition, postoperative behavioral scores were not analyzed to evaluate the possible effects of the different levels of hypothermia on cognitive function.

CONCLUSIONS

In conclusion, in patients who underwent complex proximal and total arch surgery and >30 minutes of ACP, the different deep and moderate hypothermic ranges (14.1°C-28°C) based on predicted temperature did not significantly affect short-term mortality or major morbidity, although a trend toward a greater adverse event rate was noticed in the deep hypothermia group. When we looked at actual temperature as a continuous variable, however, we found that higher temperature was significantly associated with lower stroke rates. In addition, the greater the temperature, the lower the observed incidence of reoperation for bleeding. Long-term survival appeared to be better in patients who underwent arch surgery under moderate hypothermia. This interesting finding may require further evaluation.

Conflict of Interest Statement

Dr Preventza consults for Medtronic, Inc, and participates in clinical trials for WL Gore & Associates. In the past, she has received travel expenses from both Cook, Inc, and Gore. Dr Coselli participates in clinical research trials conducted by Glaxo Smith Kline, Edwards Lifesciences, and Bolton Medical; he consults for, receives royalties and a departmental educational grant from, and participates in clinical trials for Vascutek Terumo; he consults and participates in clinical trials for Medtronic, Inc, and WL Gore & Associates; and he participates in clinical research for Cook, Inc. All other authors have nothing to disclose with regard to commercial support.

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Key Words: hypothermic circulatory arrest, deep hypothermia, moderate hypothermia, aortic arch surgery, antegrade cerebral perfusion, patient outcomes