The safety of moderate hypothermic lower body circulatory arrest with selective cerebral perfusion: A propensity score analysis

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⌨ Supplemental material is available online.

Objective: There is no common guideline on what temperature should be achieved at the lower body circulatory arrest followed by the initiation of selective cerebral perfusion.

Methods: Between October 1999 and August 2005, a total of 377 patients underwent repair of the aortic arch with selective cerebral perfusion and hypothermic circulatory arrest at 20°C to 28°C and were divided into two groups: (1) 125 patients with deep lower body circulatory arrest at 20°C to 24.9°C (deep lower body circulatory arrest group) and (2) 252 patients with moderate lower body circulatory arrest at 25°C to 28°C (moderate lower body circulatory arrest group). To compensate for the differences in patient characteristics, we used a propensity score matching analysis, and comparable patients, 92 patients from each group, were identified for final analysis.

Results: There were no significant differences in mortality or morbidity between deep and moderate lower body circulatory arrest, in either the entire study cohort or the propensity-matched cohort. C-reactive protein level 1 day after the operation approached but fell short of significance (108.4 ± 47.7 mg/L in deep lower body circulatory arrest group and 95.8 ± 44.2 mg/L in moderate lower body circulatory arrest group, $P = .07$). The mean temperatures at the initiation of lower body circulatory arrest were 24.1°C ± 2.2°C in patients who underwent reexploration for bleeding and 24.9°C ± 1.8°C in patients who did not ($P = .025$); the difference also reached statistical significance in multivariate analysis ($P = .046$, odds ratio 0.796).

Conclusions: Our results suggest that moderate lower body circulatory arrest can be safely performed for aortic arch repair. In fact, postoperative inflammatory response tended to be lower in patients with moderate lower body circulatory arrest than those with deep lower body circulatory arrest, and deep lower body circulatory arrest was a strong risk factor for reexploration for bleeding.

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Although the introduction of deep hypothermic circulatory arrest (HCA) improved surgical results of more extensive operations on the thoracic aorta,[1,2] these complex procedures are still associated with a relatively high mortality and high incidences of neurologic complications. As is well known, the safe duration of HCA alone is limited,[3-6] and HCA is therefore normally performed with the use of retrograde cerebral perfusion or antegrade selective cerebral perfusion (SCP). Because the real benefit of retrograde cerebral perfusion is not uniformly accepted,[6,7] the combination of HCA and SCP is currently adopted in many institutions. There is no common guideline as to the temperature that should be achieved before extracorporeal circulation can be stopped and followed by the initiation of SCP, however, and each institution has its own protocol.

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
HCA = hypothermic circulatory arrest
LBCA = lower body circulatory arrest
SCP = selective cerebral perfusion

Until now, discussions regarding HCA have been focused on cerebral protection and neurologic outcome. Originally, deep HCA was introduced as a method of cerebral protection, and because the brain is the most sensitive organ to ischemic injury, it is considered that the temperature should be dropped to 20°C or lower when no other adjunct cerebral protection is available. With the use of SCP, however, HCA acts as lower body circulatory arrest (LBCA), and the temperature for HCA can therefore be higher. To distinguish between HCA of the entire body and HCA of the lower body, HCA with the use of SCP is defined as LBCA in this article.

In recent years, the trend has gone from deep temperatures, cooler than 20°C as advocated by the Mount Sinai group,[6] toward temperatures as high as 25°C.[8-10] The avoidance of deep core temperatures at LBCA may offer the advantage of shorter cardiopulmonary bypass (CPB) times and reductions in coagulation disorders and the accumulation of inflammatory parameters, but it can theoretically cause ischemic injury to the visceral organs and the spinal cord.

In our institution, SCP was introduced in 1999 in combination with deep HCA at temperatures lower than 20°C. The temperature of LBCA has gone higher as we gained experience, and it is now performed at 25°C to 28°C. This temperature is clearly higher than in other institutions, where it is performed at 20° to 25°C.[8-10] It is difficult to say whether the results are acceptable, however, because previous studies had no control group regarding the temperature of LBCA. The aim of this study was to compare the in-hospital outcomes of patients with LBCA at 25°C to 28°C with those of a propensity-matched group of patients with LBCA at 20°C to 24.9°C.

Patients and Methods
Patients
Between October 1999 and August 2005, a total of 832 adult patients underwent surgery for ascending aortic disease through a median sternotomy with or without a repair of the aortic arch, and LBCA (HCA with SCP) was used in 473 cases. Among these patients, 60 who were operated on with the use of profound LBCA at a nasopharyngeal temperature lower than 20°C and 36 operated on with the use of moderate LBCA at a nasopharyngeal temperature higher than 28°C were excluded; the remaining 377 patients were retrospectively examined in this study. These 377 patients were divided into two groups according to nasopharyngeal tem-

perature at the initiation of HCA: (1) 125 patients (33.1%) underwent deep LBCA at a nasopharyngeal temperature of 20°C to 24.9°C (deep LBCA group) and (2) 252 patients (66.9%) underwent moderate LBCA at a nasopharyngeal temperature of 25°C to 28°C (moderate LBCA group). All patient characteristics were assessed and are presented in Table 1. The distribution of patients according to HCA time is shown in Figure 1.

Operative Technique
Anesthesia was induced and maintained in a standard manner. The proximal thoracic aorta was approached through a median sternotomy in all cases. After systemic heparinization, CPB was instituted with a cannula for arterial return to the aortic arch, even in cases of acute aortic dissection type A,[10] and a venous single two-stage cannula in the right atrium. The left side of the heart was vented through the right superior pulmonary vein. Myocardial protection was achieved with cold blood cardioplegia. The ascending aorta was clamped, and manipulation of the proximal site was performed. After the patient was cooled to the target temperature, the systemic circulation was arrested, the aneurysm was opened, and the arterial cannula was removed. With the patient in the Trendelenburg position, 15F retrograde coronary sinus perfusion cannulas (Medtronic DLP, Grand Rapids, Mich) connected to the oxygenator with a separate single-roller pump head were inserted into the innominate artery and the left carotid artery. The left subclavian artery was clamped or occluded with a Fogarty catheter (Baxter Healthcare Corporation, Deerfield, Ill) to avoid the steal phenomenon. For SCP, cold blood at 15°C was perfused with a circuit for blood cardioplegia. Cerebral perfusion was initiated at a rate of 10 ml/(min · kg) and adjusted to maintain a pressure between 40 and 60 mm Hg. After the aortic arch was repaired, SCP was ceased and CPB was resumed with the perfusion cannula directly reinserted into the graft. Deairing was performed in a standard manner.

Definitions of Complications
In accordance with the report by Ergin and colleagues,[5] we defined temporary neurologic dysfunction as the occurrence of at least one of the following symptoms: postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism without obvious neurologic deficit. Stroke was defined as the presence of transient or permanent focal neurologic deficit that was confirmed as a new deficit by means of computed tomography. Respiratory insufficiency was defined as prolonged intubation for more than 48 hours because of inadequate status of gas exchange. Criteria for extubation included adequate response to commands, respiratory rate greater than 12 breaths/min, end-tidal carbon dioxide tension less than 50 mm Hg, and an oxygen saturation by pulse oximetry greater than 95% at an inspired oxygen fraction of 0.3.

Statistical Analysis
Results are expressed as mean ± SD. Statistical analyses were performed with the Student t-test for continuous variables or with χ^2 tests (Fisher exact tests if n < 5) for categorical variables.

In view of the marked and significant differences in patient characteristics between the groups, patient matching seemed necessary to evaluate the genuine effects of temperature on mortality and morbidity. To compensate for the differences in this retrospec-
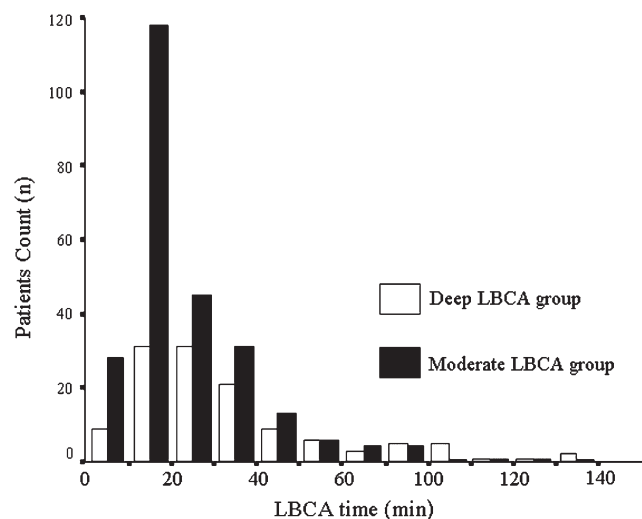
TABLE 1. Patient characteristics

	Entire study sample				Propensity-matched pairs			
	Overall	Deep LBCA	Moderate LBCA	P value	Overall	Deep LBCA	Moderate LBCA	P value
Patients (No.)	377	125	252		184	92	92	
Age (y, mean ± SD)	61.8 ± 11.8	60.9 ± 13.1	62.3 ± 11.1	.31	62.1 ± 11.2	62.2 ± 12.0	62.0 ± 10.0	.88
Male (No.)	262 (69.5%)	81 (64.8%)	181 (71.8%)	.16	123 (66.8%)	60 (65.2%)	63 (68.4%)	.63
Body mass index (kg/m^2, mean ± SD)	26.5 ± 4.1	25.6 ± 3.8	27.0 ± 4.2	.002	26.3 ± 3.6	26.2 ± 3.8	26.4 ± 3.4	.79
Reoperative case (No.)	72 (19.1%)	24 (19.2%)	48 (19.0%)	.97	33 (17.9%)	17 (18.4%)	16 (17.3%)	.84
Emergency (No.)	141 (37.4%)	55 (44.0%)	86 (34.1%)	.62	71 (38.6%)	37 (40.2%)	34 (36.9%)	.65
Type A dissection (No.)	126 (33.4%)	50 (40.0%)	76 (30.1%)	.57	66 (35.9%)	34 (36.9%)	32 (34.7%)	.75
Marfan syndrome (No.)	7 (1.9%)	6 (4.8%)	1 (0.3%)	.003	1 (0.5%)	0 (0%)	1 (1.08%)	.31
History of neurologic event (No.)								
Transient	11 (2.9%)	6 (4.8%)	5 (1.9%)	.12	4 (2.2%)	1 (1.08%)	3 (3.2%)	.31
Persistent	25 (6.6%)	7 (5.6%)	18 (7.1%)	.57	14 (7.6%)	7 (7.6%)	7 (7.6%)	>.99
Smoking history (No.)	133 (35.3%)	56 (44.8%)	77 (30.5%)	.006	82 (44.6%)	42 (45.6%)	40 (43.4%)	.76
Hypertension (No.)	291 (77.2%)	99 (79.2%)	192 (76.1%)	.51	148 (80.4%)	74 (80.4%)	74 (80.4%)	>.99
Hyperlipidemia (cholesterol >200 mg/dL, No.)	168 (44.6%)	55 (44.0%)	113 (44.8%)	.87	84 (45.7%)	41 (44.5%)	43 (46.7%)	.76
Diabetes mellitus (insulin dependent, No.)	4 (1.1%)	1 (0.8%)	3 (1.1%)	.72	2 (1.1%)	1 (2.3%)	1 (2.3%)	>.99
Chronic obstructive pulmonary disease (No.)	79 (21.0%)	28 (22.4%)	51 (20.2%)	.62	43 (23.4%)	22 (23.9%)	21 (22.8%)	.86
Peripheral arterial disease (No.)	12 (3.2%)	4 (3.2%)	8 (3.1%)	.98	9 (4.9%)	4 (4.3%)	5 (5.4%)	.73
Coronary artery disease (No.)	113 (30.0%)	29 (23.2%)	84 (33.3%)	.43	55 (29.9%)	25 (27.1%)	30 (32.6%)	.42
Chronic renal insufficiency (No.)	40 (10.6%)	11 (8.8%)	29 (11.5%)	.42	15 (8.2%)	8 (8.6%)	7 (7.6%)	.78

LCBA, Lower body circulatory arrest.

tive, nonrandomized study, we used a propensity score matching analysis. For this purpose, logistic regression was used to develop a propensity score.[11,12] The propensity score included age, sex, body mass index, reoperation, emergency operation, Marfan syndrome, previous neurologic events, smoking history, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes

Figure 1. Distribution of patients by hypothermic circulatory arrest time. *LBCA*, Lower body circulatory arrest.

mellitus (insulin dependent), peripheral vascular disease, coronary artery disease, renal insufficiency (creatinine >2.0 mg/dL), total arch replacement, concomitant operations (aortic valve root operation, coronary artery bypass grafting, mitral valve operation), duration of aortic crossclamping, and duration of LBCA. From these covariables, a propensity score was calculated for each patient. Finally, each patient in the deep LBCA group was matched with a patient in the moderate LBCA group with the closest propensity score. The maximum difference in propensity score for a match was less than 0.015. By using this novel method, comparable patient groups (92 patients from each group) were identified for final analysis (Table 1). Logistic regression was also used for the analysis of risk factors for postoperative mortality and morbidity and the effects of temperature on postoperative mortality and morbidity. All statistical analyses were performed with SPSS 10.0 software (SPSS Inc, Chicago, Ill).

Results

Analysis of the Entire Patient Population

Rate of total arch replacement was significantly higher in the deep LBCA group than in the moderate LBCA group (31% vs 19%, P = .008). This may be related to longer durations of LBCA (34.1 ± 24.4 minutes in deep LBCA group vs 23.5 ± 15.8 minutes in moderate LBCA group, P = .001), SCP (25.8 ± 18.1 vs 18.8 ± 14.2 minutes, P = .001), CPB (193.3 ± 77.9 vs 175.7 ± 67.1 minutes, P = .025), and operation (304.8 ± 112.5 vs 279.2 ± 92.6 minutes, P =

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TABLE 2. Perfusion data and postoperative morbidity and mortality

	Entire study sample				Propensity-matched pairs			
	Overall	Deep LBCA	Moderate LBCA	P value	Overall	Deep LBCA	Moderate LBCA	P value
Patients (No.)	377	125	252		184	92	92	
Mean temperature (°C, mean ± SD)	25.3 ± 1.8	23.2 ± 1.2	26.3 ± 0.9	.0001	24.8 ± 1.9	23.3 ± 1.3	26.3 ± 0.9	.0001
Total arch replacement (No.)	87 (23.1%)	39 (31.2%)	48 (19.0%)	.008	47 (25.5%)	23 (25.0%)	24 (26.0%)	.86
Duration of operation (min, mean ± SD)	287.4 ± 100.2	304.8 ± 112.5	279.2 ± 92.6	.023	292.8 ± 101.6	289.5 ± 94.8	296.1 ± 108.5	.66
Duration of cardiopulmonary bypass (min, mean ± SD)	181.4 ± 71.2	193.3 ± 77.9	175.7 ± 67.1	.025	185.2 ± 70.9	184.1 ± 69.4	186.3 ± 72.8	.83
Duration of aortic crossclamping (min, mean ± SD)	114.4 ± 40.7	117.7 ± 43.2	112.5 ± 39.4	.24	116.6 ± 41.8	114.6 ± 40.7	118.6 ± 42.9	.51
Duration of hypothermic circulatory arrest (min, mean ± SD)	27.0 ± 19.6	34.1 ± 24.4	23.5 ± 15.8	.001	28.0 ± 18.1	27.7 ± 16.1	28.4 ± 19.9	.81
Duration of selective cerebral perfusion (min, mean ± SD)	21.1 ± 15.9	25.8 ± 18.1	18.8 ± 14.2	.001	22.4 ± 16.9	22.3 ± 15.2	22.6 ± 18.4	.90
Duration of mechanical ventilation (h, mean ± SD)	70.5 ± 157.8	88.3 ± 206.0	61.7 ± 126.7	.12	74.3 ± 183.6	82.2 ± 218.6	66.5 ± 141.1	.56
Intensive care unit stay (d, mean ± SD)	4.2 ± 5.9	5.0 ± 6.7	3.8 ± 5.4	.05	4.4 ± 6.4	4.6 ± 6.6	4.1 ± 6.3	.57
In-hospital death (No.)	34 (9.0%)	14 (11.2%)	20 (7.9%)	.29	18 (9.8%)	8 (8.6%)	10 (10.8%)	.62
Stroke (No.)	23 (6.1%)	10 (8.0%)	13 (5.1%)	.27	12 (6.5%)	6 (6.5%)	6 (6.5%)	>.99
Temporary neurologic dysfunction (No.)	60 (15.9%)	28 (22.4%)	32 (12.6%)	.15	22 (12%)	13 (14.1%)	9 (9.7%)	.36
Reexploration for bleeding (No.)	58 (15.4%)	25 (20.0%)	33 (13.0%)	.08	31 (16.8%)	18 (19.5%)	13 (14.1%)	.32
Respiratory insufficiency (No.)	41 (10.9%)	14 (11.2%)	27 (10.7%)	.88	22 (12%)	11 (11.9%)	11 (11.9%)	>.99
Tracheotomy (No.)	35 (9.3%)	15 (12.0%)	20 (7.9%)	.20	16 (8.7%)	9 (9.7%)	7 (7.6%)	.60
Renal failure (No.)	30 (7.9%)	13 (4.8%)	17 (6.7%)	.48	14 (7.6%)	8 (8.6%)	6 (6.5%)	.58
Temporary dialysis (No.)	23 (6.1%)	9 (7.2%)	14 (5.5%)	.54	12 (6.5%)	6 (6.5%)	6 (6.5%)	>.99
Permanent dialysis (No.)	7 (1.9%)	4 (3.2%)	3 (1.1%)	.17	2 (1.1%)	2 (2.1%)	0 (0%)	.15
Paraplegia (No.)	8 (2.1%)	4 (3.2%)	4 (1.5%)	.30	7 (3.8%)	4 (4.3%)	3 (3.2%)	.70

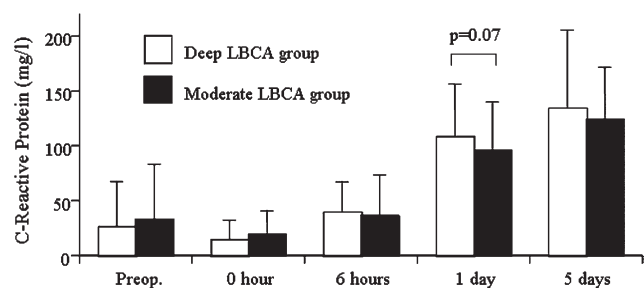*LCBA*, Lower body circulatory arrest.

.023) in the deep LBCA group than in the moderate LBCA group. Intensive care unit stay was longer in the deep LBCA group (5.0 ± 6.7 vs 3.8 ± 5.4 days, *P* = .05). In-hospital mortalities were 11.2% in the deep LBCA group and 7.9% in the moderate LBCA group (*P* = .29). There was a trend toward a higher rate of reexploration for postoperative bleeding in the deep LBCA group (20% vs 13%, *P* = .08); however, there were no differences in other complications between the groups (Table 2).

Propensity Score Matching Analysis
Baseline characteristics of propensity-matched pairs were almost identical (Table 1). There were no significant differences in CPB time (184.1 ± 69.4 in deep LBCA group vs 186.3 ± 72.8 minutes in moderate LBCA group, *P* = .83) and operative time (289.5 ± 94.8 vs 296.1 ± 108.5 minutes, *P* = .62) between the deep and moderate LBCA groups.

In-hospital mortalities were 8.6% in the deep LBCA group and 10.8% in the moderate LBCA group (*P* = .62). There was no significant difference in reexploration for postoperative bleeding between the deep and moderate LBCA groups (19.5% vs 14.1%, *P* = .32) and also no differences in any other postoperative complications between the groups (Table 2).

Time courses of the following factors were also analyzed in the propensity-matched groups: blood urea nitrogen, creatinine, and urinary output as an index of renal function; aspartate aminotransferase as an index of liver injury; creatine kinase as an index of muscle injury; lactate as an index of whole-body ischemic injury; C-reactive protein as an index of inflammatory response; and ratio of arterial to inspired oxygen concentration as an index of gas exchange function (Appendix Table E1). Only the difference in C-reactive protein

Figure 2. Time course of C-reactive protein in propensity-matched groups. *LBCA,* Lower body circulatory arrest; *Preop.,* preoperative.

level at 1 day after the operation approached (but did not reach) statistical significance (108.4 $\pm$ 47.7 mg/L in deep LBCA group vs 95.8 $\pm$ 44.2 mg/L in moderate LBCA group, P = .07; Figure 2).

Subanalysis 1: Patients With LBCA Longer Than 60 Minutes

As shown in Figure 1, most of the patients underwent LBCA for less than 60 minutes, and only 27 (7%) patients underwent LBCA for longer than 60 minutes. Prolonged LBCA can theoretically lead to higher mortality, and prolonged LBCA at higher temperature appears to be dangerous; an additional subanalysis was therefore performed on the entire

patient population to examine any effects of the temperature at the initiation of LBCA on the outcomes of patients with LBCA duration longer than 60 minutes. Mortalities were 19% (5/27 patients) among patients who underwent LBCA for longer than 60 minutes and 8% (29/350 patients) among those with LBCA less than 60 minutes (P = .08). Among the 27 patients with LBCA longer than 60 minutes, mortalities were 12.5% in the deep LBCA group and 27.3% in the moderate LBCA group (P = .33). There was a trend toward higher occurrence of paraplegia in the moderate LBCA group (0% in deep LBCA group and 18% in moderate LBCA group, P = .08). There were no significant differences in any other postoperative complications (Table 3).

Subanalysis 2: Acute Aortic Dissection Type A

Emergency operation for acute aortic dissection type A was a strong risk factor for mortality. In the entire study cohort, the mortalities were 5.6% among patients with nonacute dissection and 15.9% among those with acute dissection (P = .001). To examine the effects of the temperature at LBCA on outcomes in this high-risk cohort, a subanalysis was performed on the entire patient population. There were no differences in perfusion data (CPB, aortic crossclamping, HCA, and SCP times). Mortalities were 18% (9/50 patients) in the deep LBCA group and 14.5% (11/76 patients) in the moderate LBCA group (P = .59). There were no significant differences in rates of any postoperative complications between the groups (Table 4).

TABLE 3. Subanalysis: Patients with hypothermic circulatory arrest longer than 60 minutes

	Overall	Deep LBCA	Moderate LBCA	P value
Patients (No.)	27	16	11	
Age (y, mean $\pm$ SD)	56.5 $\pm$ 12.2	53.7 $\pm$ 12.3	60.6 $\pm$ 11.4	.15
Male (No.)	22 (81.5%)	12 (75.0%)	10 (90.9%)	.29
Type A dissection (No.)	12 (44.4%)	4 (25.0%)	8 (72.7%)	.014
Aortic valve root operation (No.)	10 (37.0%)	4 (25.0%)	6 (54.5%)	.12
Coronary artery bypass grafting (No.)	4 (14.8%)	2 (12.5%)	2 (18.2%)	.68
Total arch replacement (No.)	23 (85.2%)	12 (75.0%)	11 (100%)	.07
Duration of operation (min, mean $\pm$ SD)	364.7 $\pm$ 136.1	390.8 $\pm$ 166.2	326.8 $\pm$ 63.6	.26
Duration of cardiopulmonary bypass (min, mean $\pm$ SD)	243.9 $\pm$ 94.2	266.6 $\pm$ 112.2	210.8 $\pm$ 46.5	.13
Duration of aortic crossclamping (min, mean $\pm$ SD)	132.5 $\pm$ 60.5	127.2 $\pm$ 68.7	140.2 $\pm$ 48.3	.59
Duration of hypothermic circulatory arrest (min, mean $\pm$ SD)	80.6 $\pm$ 20.2	85.3 $\pm$ 22.5	73.8 $\pm$ 14.7	.15
Duration of selective cerebral perfusion (min, mean $\pm$ SD)	63.1 $\pm$ 13.2	61.8 $\pm$ 11.9	64.9 $\pm$ 15.2	.56
Reexploration for bleeding (No.)	9 (33.3%)	7 (43.8%)	2 (18.2%)	.16
Duration of mechanical ventilation (h, mean $\pm$ SD)	184.0 $\pm$ 270.4	155.1 $\pm$ 223.4	226.2 $\pm$ 334.6	.51
Intensive care unit stay (d, mean $\pm$ SD)	9.2 $\pm$ 11.5	7.8 $\pm$ 9.0	11.2 $\pm$ 14.6	.44
In-hospital death (No.)	5 (18.5%)	2 (12.5%)	3 (27.3%)	.33
Stroke (No.)	6 (22.2%)	3 (18.8%)	3 (27.3%)	.60
Temporary neurologic dysfunction (No.)	6 (22.2%)	5 (31.3%)	1 (9.1%)	.17
Respiratory insufficiency (No.)	6 (22.2%)	4 (25.0%)	2 (18.2%)	.68
Postoperative use of dialysis (No.)	4 (14.8%)	2 (12.5%)	2 (18.2%)	.68
Paraplegia (No.)	2 (7.4%)	0 (0%)	2 (18.2%)	.08

LCBA, Lower body circulatory arrest.

TABLE 4. Subanalysis: Patients with acute aortic dissection type A

	Overall	Deep LBCA	Moderate LBCA	P
Patients (No.)	126	50	76	
Age (y, mean ± SD)	60.6 ± 12.7	59.0 ± 15.3	61.7 ± 10.8	.24
Male (No.)	92 (73.0%)	36 (72.0%)	56 (73.6%)	.83
Aortic valve-root operation (No.)	79.0 (62.7%)	30 (60.0%)	49 (64.4%)	.61
Coronary artery bypass grafting (No.)	13 (10.3%)	2 (4.0%)	11 (14.5%)	.06
Total arch replacement (No.)	34 (27.0%)	12 (24.0%)	22 (28.9%)	.54
Duration of operation (min, mean ± SD)	289.2 ± 102.7	286.6 ± 121.9	291.0 ± 88.7	.81
Duration of cardiopulmonary bypass (min, mean ± SD)	194.6 ± 76.5	194.1 ± 89.1	194.9 ± 67.7	.95
Duration of aortic crossclamping (min, mean ± SD)	125.9 ± 44.5	128.7 ± 47.5	124.1 ± 42.7	.57
Duration of hypothermic circulatory arrest (min, mean ± SD)	33.6 ± 16.0	33.5 ± 15.9	33.8 ± 16.3	.91
Duration of selective cerebral perfusion (min, mean ± SD)	27.5 ± 14.8	26.7 ± 14.3	27.9 ± 15.2	.65
Reexploration for bleeding (No.)	28 (22.2%)	13 (26.0%)	15 (19.7%)	.41
Duration of mechanical ventilation (h, mean ± SD)	101.3 ± 167.8	79.0 ± 131.1	116.1 ± 187.4	.22
Intensive care unit stay (d, mean ± SD)	5.7 ± 6.9	5.2 ± 5.5	6.0 ± 7.7	.52
In-hospital death (No.)	20 (15.9%)	9 (18.0%)	11 (14.5%)	.59
Stroke (No.)	10 (7.9%)	5 (10.0%)	5 (6.6%)	.49
Temporary neurologic dysfunction (No.)	29 (23.0%)	15 (30.0%)	14 (18.4%)	.13
Respiratory insufficiency (No.)	20 (15.9%)	6 (6.0%)	14 (22.3%)	.34
Postoperative use of dialysis (No.)	19 (15.1%)	7 (14.0%)	12 (15.8%)	.78
Paraplegia (No.)	6 (4.8%)	3 (6.0%)	3 (3.9%)	.6

LCBA, Lower body circulatory arrest.

Risk Factors for Postoperative Mortality and Morbidity

To detect risk factors for postoperative mortality and morbidity in our study cohort, multivariate analyses were performed (Table 5). In these analyses, CPB and LBCA times were treated as a continuous variable, and the odds ratio reflected per degree risk. The temperature was also treated as a continuous variable, and the odds ratio therefore reflected per degree risk. Prolonged CPB was strongly associated with most postoperative adverse events, and the tem-

TABLE 5. Risk factors for postoperative mortality and morbidity analyzed with multivariate logistic regression

	Entire study sample	Propensity-matched sample
Mortality	CPB time (P = .0001), OR 1.011, 95% CI 1.007-1.016	CPB time (P = .001), OR 1.011 95% CI 1.004-1.018
		Reoperative case (P = .014), OR 6.666 95% CI 1.457-30.439
Temporary neurologic dysfunction	Age (P = .003), OR 1.046, 95% CI 1.016-1.077	None
	Total arch replacement (P = .008), OR 3.834 95% CI 1.422-10.339	
	LBCA time (P = .005), OR 1.029 95% CI 1.009-1.049	
Stroke	CPB time (P = .006), OR 1.006, 95% CI 1.002-1.013	CPB time (P = .006), OR 1.011 95% CI 1.003-1.019
	LBCA time (P = .008), OR 1.030, 95% CI 1.008-1.053	LBCA time (P = .028), OR 1.056 95% CI 1.006-1.109
Reexploration for bleeding	CPB time (P = .002), OR 1.006, 95% CI 1.002-1.010	CPB time (P = .004), OR 1.009 95% CI 1.003-1.015
		Reoperative case (P = .014), OR 3.902 95% CI 1.324-11.497
		Temperature (P = .046), OR 0.796 95% CI 0.636-0.996
Respiratory failure	Reoperative case (P = .005), OR 3.637 95% CI 1.484-8.910	Reoperative case (P = .037), OR 3.896 95% CI 1.086-13.977
	CPB time (P = .002), OR 1.007 95% CI 1.002-1.011	CPB time (P = .0001), OR 1.011 95% CI 1.005-1.017
	Age (P = .002), OR 1.063 95% CI 1.024-1.104	
Postoperative dialysis	Age (P = .002), OR 1.074 95% CI 1.027-1.124	Age (P = .024), OR 1.089 95% CI 1.011-1.174
	CPB time (P = .005), OR 1.007 95% CI 1.002-1.012	CPB time (P = .004), OR 1.012 95% CI 1.004-1.021)
Paraplegia	None	BMI (P = .019), OR 1.315 95% CI 1.045-1.654

CPB, Cardiopulmonary bypass; *OR*, odds ratio; *CI*, confidence interval; *LBCA*, lower body circulatory arrest; *BMI*, body mass index.

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TABLE 6. Association between postoperative complications and temperature

Variable	Status	Entire study sample					Status	Propensity-matched sample				
		Mean temp (°C)	Uni P value	Multi P value	OR	95% CI		Mean temp (°C)	Uni P value	Multi P value	OR	95% CI
Mortality	Dead (n = 34)	24.9 ± 2.1	.13	.91	0.98	0.752-1.292	Dead (n = 18)	24.8 ± 2.0	.94	.587	1.090	0.799-1.485
	Survived (n = 343)	25.4 ± 1.7					Survived (n = 166)	24.9 ± 1.9				
TND	Yes (n = 52)	25.1 ± 1.7	.24	.76	0.97	0.179-1.184	Yes (n = 22)	24.9 ± 1.6	.66	.441	1.108	0.854-0.147
	No (n = 325)	25.4 ± 1.8					No (n = 162)	24.8 ± 1.9				
Stroke	Yes (n = 23)	24.9 ± 2.1	.37	.82	1.04	0.733-1.479	Yes (n = 12)	24.7 ± 2.2	.86	.982	1.004	0.691-1.460
	No (n = 354)	25.3 ± 1.8					No (n = 172)	24.8 ± 1.9				
Reexploration for bleeding	Yes (n = 58)	24.9 ± 2.2	.05	.39	0.92	0.754-1.117	Yes (n = 31)	24.1 ± 2.2	.03	.046	0.796	0.636-0.996
	No (n = 319)	25.4 ± 1.7					No (n = 153)	24.9 ± 1.8				
Respiratory failure	Yes (n = 40)	25.1 ± 1.8	.40	.45	1.10	0.852-1.430	Yes (n = 22)	24.6 ± 2.1	.59	.839	1.029	0.779-1.360
	No (n = 337)	25.3 ± 1.8					No (n = 162)	24.8 ± 1.8				
Postoperative dialysis	Yes (n = 28)	24.8 ± 1.8	.12	.17	0.80	0.581-1.103	Yes (n = 14)	24.3 ± 1.7	.30	.298	0.841	0.607-1.165
	No (n = 349)	25.4 ± 1.8					No (n = 170)	24.8 ± 1.9				
Paraplegia	Yes (n = 8)	24.2 ± 2.2	.08	NA	NA	NA	Yes (n = 7)	23.9 ± 2.2	.20	NA	NA	NA
	No (n = 369)	25.3 ± 1.8					No (n = 177)	24.8 ± 2.2				

temp, Temperature; *Uni*, univariate; *Multi*, multivariate; *OR*, Odds ratio; *CI*, confidence interval; *TND*, temporary neurologic dysfunction; *NA*, not available.

perature was only statistically significantly associated with reexploration for bleeding. Paraplegia, an uncommon yet critical complication in arch replacement, was seen in 8 patients in our study cohort. In these analyses, no risk factors could be identified in the entire study cohort, and body mass index was the only risk factor for postoperative paraplegia in the propensity-matched cohort.

Associations Between Postoperative Complications and Temperature
To examine associations between postoperative complications and the temperature at the initiation of LBCA, univariate and multivariate analyses were performed (Table 6). In these analyses, the temperature was treated as a continuous variable and the odds ratio therefore reflected per degree risk. Reexploration for bleeding was the only factor significantly associated with temperature. In the entire study sample, the mean temperatures at the initiation of LBCA were 24.9°C ± 2.2°C among patients who underwent reexploration and 25.4°C ± 1.7°C among those without it ($P = .046$), but this difference did not reach statistical significance in the multivariate analysis ($P = .39$). In the propensity-matched cohort, the mean temperatures at the initiation of LBCA were 24.1°C ± 2.2°C among patients who underwent reexploration and 24.9°C ± 1.8°C among those without it ($P = .025$); this difference also reached statistical significance in the multivariate analysis ($P = .046$, odds ratio, 0.796). For the occurrence of paraplegia, multivariate analysis could not be performed because of the low number of events.

Discussion
In this study, there were no significant differences in mortality or morbidity between deep and moderate LBCA in either the entire study cohort or the propensity-matched cohort. There was a trend toward lower postoperative inflammatory response in patients with moderate LBCA, however, which fell short of reaching statistical significance, and deep LBCA was strongly associated with reexploration for bleeding.

At the beginning of this study, we found the differences in the distribution of patient baseline data to be too great for a proper analysis. Patients with deep LBCA had lower body mass index, greater incidence of Marfan syndrome, and more smoking history. Moreover, they underwent fewer concomitant procedures (Appendix Table E2), more total arch replacement, and longer duration of LBCA. To generate a reasonable control group, propensity matching was performed for this study.[12,13] Because LBCA and aortic crossclamping times are dependent on the surgical procedure and independent of the temperature at the initiation of LBCA, both factors were included in the matching process. Operative and CPB times were not included in this process, because we considered those factors to be dependent on LBCA, aortic crossclamping, cooling, rewarming, and hemostasis times.

Against our speculation, there were no differences in CPB and operative times between the groups in the propensity-matched cohort. Generally, it is considered that deep hypothermia is associated with prolonged CPB,[7] and Harrington and associates[14] reported that mean CPB times were 191 ± 53

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minutes in a deep hypothermic CPB group and 131 ± 48 minutes in a moderate hypothermic CPB group ($P < .0001$), with their deep hypothermic CPB group undergoing HCA for 31 ± 14 minutes. Theoretically, longer cooling and rewarming times are required for deep HCA; in our series, however, 75% of patients underwent concomitant procedures during the cooling and rewarming phases. This may account for the lack of differences in CPB and operative times between the two groups.

As we speculated, there were no differences in neurologic adverse event between the groups in any analysis. SCP protocol was identical in the two groups, and hypothermia was only needed as a brain protection during the period from the termination of CPB to the initiation of SCP and from the termination of SCP to the resumption of CPB. In our series, the difference between HCA and SCP times was approximately 6 minutes. Our data suggest that the difference in temperature at LBCA does not affect the quality of cerebral protection during this period.

Although the spinal cord consists of neural cells such as are present in the cerebrum and is most likely sensitive to ischemic damage in a similar manner as in the brain, the occurrences of paraplegia were similar in the two groups. This outcome may have been due to our institutional perfusion protocol. We performed SCP with cold blood at 15°C, and it was observed in general that the nasopharyngeal temperature would continue to fall during the LBCA period, commonly dropping to 20°C, although the temperature of the bladder would remain at the temperature at the initiation of LBCA. The mechanism of this phenomenon is unclear, but perhaps it was caused by the collateral blood flow through the vertebral artery and the returned cool blood from the head to the right atrium. It can be speculated that this cooling phenomenon acted protectively for the spinal cord and therefore resulted in a relatively low incidence of paraplegia among patients with moderate LBCA.

There were also no differences in the biologic parameters of any other organs. Similar to our results, Harrington and associates[14] concluded that hypothermic CPB is not a risk factor for renal or early pulmonary dysfunction. Generally, visceral organs, including the lungs, can tolerate ischemic damage better than can the brain or the heart. Our results suggest that visceral organs can be well protected by moderate LBCA.

In this series, only the difference in C-reactive protein level 1 day after the operation approached statistical significance ($P = .08$). The actual adverse effects of deep hypothermia on inflammatory response have not been made clear, but our results suggest that deep LBCA may activate inflammatory response, as others have already speculated.[7,15] This issue, however, appears to be difficult to prove in a clinical setting. In this series there were no

differences in any clinical outcomes except reexploration for bleeding.

It is well known that coagulopathy is induced by hypothermia[16,17] but it has been difficult to prove this association in a clinical setting, especially with regard to HCA, as seen in the report by Harrington and associates[14] in which profound hypothermia was not associated with increased postoperative hemorrhage in their comparative study of deep HCA.[14] In our study, reexploration for bleeding was the only factor significantly associated with temperature. This result suggests that the use of deep LBCA can possibly cause postoperative bleeding.

Generally, acute aortic dissection type A is associated with high mortality, and this was also the case in our series. Even in this high-risk cohort, however, there were no differences in clinical outcome between the two groups. Our results demonstrate that moderate LBCA is a safe strategy for the treatment of acute aortic dissection type A.

Among the patients who underwent HCA for longer than 60 minutes, 2 patients (1 with acute aortic dissection type A and 1 without it) who underwent moderate LBCA had paraplegia occur, whereas none of those who underwent deep LBCA did ($P = .08$). There were neither significant differences nor any trends toward significance in any other postoperative adverse effects. In our entire study cohort, only 7% of the patients (n = 27) underwent LBCA for longer than 60 minutes, as shown in Figure 1, and this patient volume was too small to conclude anything from a subanalysis. On the other hand, LBCA time was 50.2 ± 20.7 minutes among patients who underwent total arch replacement and 20.4 ± 13.1 minutes among patients who underwent hemiarch replacement ($P = .0001$), and the percentages of paraplegia were 4.7% (4/85 patients) and 1.4% (4/292 patients), respectively ($P = .064$). In our institution, arch vessels are commonly reconstructed as an island, and this might explain why most of the cases were completed with less than 60 minutes of LBCA. Here it should be strongly emphasized that the results of this study do not support the suggestion that moderate LBCA has no time limit, and this method should not be used for patients who require complex total arch replacement with individual arch vessel reconstruction.

Unfortunately, we could not find the optimal temperature for LBCA and consider this a study limitation. The LBCA temperature ranged mainly from 25°C to 28°C, and the optimal temperature could not be identified with this concentration in distribution in our preliminary pilot study. The temperature of 25°C to 28°C is quite higher than reported in other institutions,[8-10] however, and we believe that it is meaningful to analyze and discuss the safety of LBCA in this temperature range.

In conclusion, there were no significant differences in mortality or morbidity between deep and moderate LBCA

in either the entire study cohort or the propensity-matched cohort. There was a trend toward lower postoperative inflammatory response in patients with moderate LBCA, however, and deep LBCA was strongly associated with reexploration for bleeding. Our results suggest that moderate LBCA can be safely performed for aortic arch repair for 60 minutes or less. It remains unclear whether it is safe beyond 60 minutes.

References

1. Svensson LG, Crawford ES, Hess KR, Coselli JS, Raskin S, Shenaq SA, et al. Deep hypothermia with circulatory arrest. Determinants of stroke and early mortality in 656 patients. *J Thorac Cardiovasc Surg.* 1993;106:19-28.
2. Griepp RB, Ergin MA, McCullough JN, Nguyen KH, Juvonen T, Chang N, et al. Use of hypothermic circulatory arrest for cerebral protection during aortic surgery. *J Card Surg.* 1997;12(2 Suppl):312-21.
3. Mezrow CK, Midulla PS, Sadeghi AM, Gandsas A, Wang W, Dapunt OE, et al. Evaluation of cerebral metabolism and quantitative electroencephalography after hypothermic circulatory arrest and low-flow cardiopulmonary bypass at different temperatures. *J Thorac Cardiovasc Surg.* 1994;107:1006-19.
4. McCullough JN, Zhang N, Reich DL, Juvonen TS, Klein JJ, Spielvogel D, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. *Ann Thorac Surg.* 1999;67:1895-9.
5. Ergin MA, Galla JD, Lansman SL, Quintana C, Bodian C, Griepp RB, Hypothermic circulatory arrest in operations on the thoracic aorta. Determinants of operative mortality and neurologic outcome. *J Thorac Cardiovasc Surg.* 1994;107:788-99.
6. Hagl C, Ergin MA, Galla JD, Lansman SL, McCullough JN, Spielvogel D, et al. Neurologic outcome after ascending aorta-aortic arch operations: effect of brain protection technique in high-risk patients. *J Thorac Cardiovasc Surg.* 2001;121:1107-21.
7. Hagl C, Khaladj N, Karck M, Kallenbach K, Leyh R, Winterhalter M, et al. Hypothermic circulatory arrest during ascending and aortic arch surgery: the theoretical impact of different cerebral perfusion techniques and other methods of cerebral protection. *Eur J Cardiothorac Surg.* 2003;24:371-8.
8. Bachet J, Guilmet D, Goudot B, Dreyfus GD, Delentdecker P, Brodaty D, et al. Antegrade cerebral perfusion with cold blood: a 13-year experience. *Ann Thorac Surg.* 1999;67:1874-8.
9. Kazui T, Kimura N, Komatsu S. Surgical treatment of aortic arch aneurysms using selective cerebral perfusion. Experience with 100 patients. *Eur J Cardiothorac Surg.* 1995;9:491-5.
10. Di Eusanio M, Schepens MA, Morshuis WJ, Di Bartolomeo R, Pierangeli A, Dossche KM. Antegrade selective cerebral perfusion during operations on the thoracic aorta: factors influencing survival and neurologic outcome in 413 patients. *J Thorac Cardiovasc Surg.* 2002;124:1080-6.
11. Minatoya K, Karck M, Szpakowski E, Harringer W, Haverich A. Ascending aortic cannulation for Stanford type A acute aortic dissection: another option. *J Thorac Cardiovasc Surg.* 2003;125:952-3.
12. Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg.* 2002;123:8-15.
13. Kunihara T, Grun T, Aicher D, Langer F, Adam O, Wendler O, et al. Hypothermic circulatory arrest is not a risk factor for neurologic morbidity in aortic surgery: a propensity score analysis. *J Thorac Cardiovasc Surg.* 2005;130:712-8.
14. Harrington DK, Lilley JP, Rooney SJ, Bonser RS. Nonneurologic morbidity and profound hypothermia in aortic surgery. *Ann Thorac Surg.* 2004;78:596-601.
15. Takano H, Sakakibara T, Matsuwaka R, Hori T, Sakagoshi N, Shinohara N. The safety and usefulness of cool head-warm body perfusion in aortic surgery. *Eur J Cardiothorac Surg.* 2000;18:262-9.
16. Reed RL 2nd, Bracey AW Jr, Hudson JD, Miller TA, Fischer RP. Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels. *Circ Shock.* 1990;32:141-52.
17. Mora Mangano CT, Neville MJ, Hsu PH, Mignea I, King J, Miller DC. Aprotinin, blood loss, and renal dysfunction in deep hypothermic circulatory arrest. Circulation. 2001;104(12 Suppl 1):I276-81.

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Appendix TABLE E1.
Perioperative parameters from propensity-matched cohort

	Deep LBCA	Moderate LBCA	*P* value
Blood urea nitrogen (mmol/L)			
Preoperative	6.7 ± 2.8	6.9 ± 3.7	.79
0 h after operation	6.7 ± 3.0	6.6 ± 2.6	.93
6 h after operation	7.5 ± 3.1	7.3 ± 2.9	.77
1 d after operation	9.2 ± 3.9	8.9 ± 4.1	.69
5 d after operation	9.7 ± 6.1	10.4 ± 7.3	.55
Creatinine (μmol/L)			
Preoperative	90.9 ± 49.2	97.9 ± 52.7	.36
0 h after operation	91.0 ± 49.2	89.9 ± 27.4	.85
6 h after operation	103.3 ± 53.5	98.7 ± 40.3	.52
1 d after operation	119.7 ± 78.6	117.5 ± 74.8	.84
5 d after operation	103.5 ± 72.2	105.8 ± 81.0	.85
Aspartate aminotransferase (U/L)			
Preoperative	29.3 ± 97.6	37.2 ± 81.3	.57
0 h after operation	53.5 ± 79.5	63.1 ± 90.3	.55
6 h after operation	79.9 ± 125.9	94.7 ± 110.5	.46
1 d after operation	116.1 ± 250.4	103.9 ± 162.4	.71
5 d after operation	91.0 ± 49.2	91.0 ± 49.2	.50
Creatine kinase (U/L)			
Preoperative	66.6 ± 61.8	101.0 ± 293.8	.30
0 h after operation	338.6 ± 376.7	302.4 ± 301.1	.48
6 h after operation	538.2 ± 643.8	735.3 ± 2062.2	.39
1 d after operation	771.2 ± 1087.2	1215.2 ± 3567.1	.26
5 d after operation	284.8 ± 840.9	280.2 ± 708.7	.97
Lactate (mmol/L)			
Preoperative	2.8 ± 1.2	2.3 ± 1.7	.60
0 h after operation	6.4 ± 4.1	5.9 ± 3.0	.63
6 h after operation	5.5 ± 3.6	5.5 ± 3.8	.97
1 d after operation	3.2 ± 2.9	3.2 ± 3.6	.94
5 d after operation	1.5 ± 1.0	1.4. ± 0.72	.93
C-reactive protein (mg/L)			
Preoperative	26.5 ± 40.9	33.2 ± 49.8	.45
0 h after operation	14.5 ± 17.5	19.0 ± 21.7	.31
6 h after operation	39.5 ± 27.4	36.7 ± 36.8	.63
1 d after operation	108.4 ± 47.7	95.8 ± 44.2	.07
5 d after operation	134.2 ± 71.1	123.8 ± 47.6	.31
Arterial oxygen fraction/inspired oxygen fraction			
Preoperative	377.9 ± 110.7	369.9 ± 116.1	.65
0 h after operation	345.3 ± 125.7	335.9 ± 131.3	.64
6 h after operation	325.8 ± 123.9	321.6 ± 105.6	.81
Urinary output first 24 h (mL)	2556.1 ± 1016.3	2694.2 ± 1351.7	.44

All data are mean ± SD. *LCBA,* Lower body circulatory arrest.

Appendix TABLE E2.
Concomitant operations

	Entire study sample				Propensity-matched pairs			
	Overall	Deep LBCA	Moderate LBCA	*P* value	Overall	Deep LBCA	Moderate LBCA	*P* value
Concomitant operation	280 (74.3%)	85 (68.0%)	195 (77.3%)	.05	138 (75.0%)	69 (75.0%)	69 (75.0%)	>.99
Aortic valve root operation	252 (66.8%)	76 (60.8%)	176 (69.8%)	.79	122 (66.3%)	61 (66.3%)	61 (66.3%)	>.99
Coronary artery bypass grafting	80 (21.2%)	19 (15.2%)	61 (24.2%)	.44	32 (17.4%)	14 (15.2%)	18 (19.5%)	.43
Mitral valve operation	6 (1.6%)	0 (0%)	6 (2.3%)	.82	0 (0%)	0 (0%)	0 (0%)	

All data are numbers and percentages of patients. *LCBA*, Lower body circulatory arrest.

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