Aortic arch surgery with hypothermic circulatory arrest and unilateral antegrade cerebral perfusion: Perioperative outcomes

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ABSTRACT

Objective: The study objective was to determine the effects of surgical procedures, circulatory management strategies, and cerebral protection strategies on the short-term outcomes of aortic arch surgery based on the 7-year clinical experience of a single center.

Methods: We analyzed the data of 1708 patients who underwent aortic arch surgery with definite hypothermic circulatory arrest and unilateral antegrade cerebral perfusion at Beijing Anzhen Hospital between 2009 and 2015. Logistic regression and random Forest regression analyses were used to determine predictors and their effects on outcomes.

Results: Thirty-day mortality was 6.1%. Permanent neurologic dysfunction incidence was 4.8%. The proportion of patients requiring continuous renal replacement therapy was 7.9%. In multivariable analyses, age, DeBakey type I dissection, New York Heart Association score, coma, coronary artery bypass grafting, extra-anatomic bypass, and cardiopulmonary bypass time were independent risk factors for mortality. Age, DeBakey type I dissection, and cardiopulmonary bypass time were independent risk factors for permanent neurologic dysfunction. In the random Forest regression, the risk for permanent neurologic dysfunction and mortality increased when unilateral antegrade cerebral perfusion time was more than 38 minutes and decreased with an increase in nasopharyngeal temperature when temperature was lower than approximately 24°C. The risk for permanent neurologic dysfunction, continuous renal replacement therapy, and paraplegia increased when temperature was greater than approximately 24°C.

Conclusions: The study showed that the largest reported cohort of patients undergoing aortic arch surgery with hypothermic circulatory arrest and unilateral antegrade cerebral perfusion had reasonable morbidity and mortality rates. As a cerebral protection strategy, unilateral antegrade cerebral perfusion may have a 38-minute safety threshold. Moderate hypothermia should be maintained below 24°C to reduce the risk for permanent neurologic dysfunction, paraplegia, and acute renal dysfunction requiring continuous renal replacement therapy. (*J Thorac Cardiovasc Surg* 2020;159:374-87)

Probability for end points with prolonged unilateral antegrade cerebral perfusion times.

Central Message

This study explored the surgical experience and short-term outcomes of 1708 patients who underwent aortic arch surgery with unilateral antegrade cerebral perfusion at Beijing Anzhen Hospital.

Perspective

By reporting the short-term outcomes of the largest cohort of patients undergoing aortic arch surgery with hypothermic circulatory arrest and unilateral antegrade cerebral perfusion, this study seeks to provide insight into the relationship between circulatory management or cerebral protection strategies and clinical outcomes and to guide surgeons in choosing optimal intraoperative strategies.

See Commentaries on pages 388 and 390.

Surgical treatment of complex aortic diseases, such as acute dissection and aneurysms involving the transverse arch, remains one of the most technically challenging endeavors

of modern aortic surgery. Although surgical procedures have evolved significantly, they still carry a high risk of morbidity and mortality.¹ Permanent neurologic

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Funded by The National Key Research and Development Program of China (2016YFC1301001, to X.H.).

Received for publication April 15, 2018; revisions received Jan 24, 2019; accepted for publication Jan 31, 2019; available ahead of print March 15, 2019.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.01.127>

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
CRRT	= continuous renal replacement therapy
LBCA	= lower-body circulatory arrest
NYHA	= New York Heart Association
OR	= odds ratio
RFR	= random Forest regression

Scanning this QR code will take you to the article title page to access supplementary information.

dysfunction is the most common complication and the leading cause of death associated with these procedures.¹ Over the past 2 decades, surgeons have continued to optimize surgical procedures, circulatory management, and cerebral protection strategies. To date, the choice of surgical procedure, circulatory management strategy, and cerebral protection strategy in patients who require aortic arch surgery remain controversial in many centers with extensive surgical experience.²⁻⁴ There is a scarcity of studies that report the relationship between these factors and clinical outcomes in large cohorts of patients undergoing aortic arch surgery.

The present retrospective study sought to document the demographic data and clinical outcomes of patients who have undergone aortic arch surgery in our center, as well as the surgical procedures and circulatory management strategies used in these patients, and to determine risk factors for 30-day mortality, postoperative permanent neurologic dysfunction, and acute renal dysfunction requiring continuous renal replacement therapy (CRRT).

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University (No. 2017016X).

Data Collection

We conducted a retrospective analysis of data collected prospectively (from January 1, 2009, to January 1, 2016) at the medical center for aortic disease of Anzhen Hospital in Beijing. The preoperative and intraoperative data of a consecutive series of 1861 adult patients who underwent aortic arch surgery were collected. We excluded patients who (1) underwent hypothermic circulatory arrest alone ($n = 148$) or hypothermic circulatory arrest with bilateral antegrade cerebral perfusion ($n = 2$) or (2) were pregnant ($n = 3$). We analyzed the remaining data of 1708 patients who underwent aortic arch surgery with definite hypothermic circulatory arrest and unilateral antegrade cerebral perfusion during this period.

VIDEO 1. Total arch replacement and frozen elephant trunk. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30362-9/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30362-9/fulltext).

Surgical Techniques

The procedures were selected on the basis of the surgical indications of the patients included in the study. Surgical indications and procedures are as follows: Total arch replacement was performed in patients with type A dissection if (1) the primary tear was in the transverse arch or the descending aorta; (2) an aneurysm was present in the aortic arch or the distal aorta (aneurysm size ≥ 40 mm); (3) the brachiocephalic artery was involved or presented with aneurysm or occlusion; or (4) the patient had Marfan syndrome. If aortic dissection extended beyond the distal arch, a frozen elephant trunk was implanted into the distal aorta. Total arch replacement was not performed in patients with type A dissection with the primary tear in the ascending aorta without the features mentioned; these patients underwent only hemiarch replacement and ascending aortic replacement.⁵

The procedure of total arch replacement and frozen elephant trunk is shown in Video 1. In all cases, general anesthesia was induced with the patient in the supine position. Blood pressure in the left radial artery and left femoral artery was monitored. All procedures were performed using a median sternotomy and total cardiopulmonary bypass (CPB) with unilateral antegrade cerebral perfusion. The right axillary artery was the preferred inflow site for CPB and unilateral antegrade cerebral perfusion. After heparinization, CPB was initiated with a flow of 2.0 to 2.4 L/m²/min, and systemic cooling was used to induce hypothermia. Arterial blood pH was managed with an alpha-stat strategy. During the cooling phase, the ascending aorta (and the aortic root or valve in some patients) was replaced and other concomitant procedures were performed, if indicated. When the nasopharyngeal temperature reached 18°C to 28°C, the 3 vessels of the arch were crossclamped (the arch vessels were also crossclamped in hemiarch replacement to prevent residual blood from interfering with the procedure) and lower-body circulatory arrest (LBCA) with unilateral antegrade cerebral perfusion was instituted. The cerebral perfusion flow rate was controlled at 5 to 10 mL/kg/min, allowing for a perfusion pressure on the pump at 50 to 80 mm Hg. During the frozen elephant trunk procedure and total arch replacement using a 4-branched graft, distal reperfusion was initiated once the distal anastomosis was completed to minimize the duration of cerebral and spinal cord ischemia. The left carotid artery was reconstructed first (after which rewarming was initiated and the brain was perfused bilaterally), followed by the ascending aorta (to resume myocardial perfusion). The left subclavian artery was repaired, and, last, the innominate artery was repaired. After completion of the repair and adequate rewarming, the patient was weaned from CPB, and the perfusion limb of the tetrafurcated graft was ligated and divided. The remainder of the procedure, including securing hemostasis and sternal closure, was performed in a routine manner.⁶

Definitions

The primary outcome measure was 30-day mortality. The secondary outcomes included in-hospital mortality and postoperative complications. Postoperative permanent neurologic dysfunction included stroke and

TABLE 1. Preoperative and intraoperative conditions of all patients

Name	Total N = 1708
Sex (male)	1282 (75.1)
Age (y)	47 (40-56)
Body mass index (kg/m ²)	25.1 (22.9-27.4)
Pathological type	
Aortic dissection	1547 (90.6)
Acute	893 (57.8)
Time onset to operation (d)	2 (1-6)
Time onset to diagnosis (d)	2 (1-3)
Subacute	273 (17.6)
Chronic	381 (24.6)
DeBakey	
I	1339 (86.6)
II	208 (13.4)
Aortic aneurysm	135 (7.9)
Pseudoaneurysm	26 (1.5)
NYHA score	
I	45 (2.6)
II	682 (39.9)
III	912 (53.4)
IV	69 (4.0)
Left ventricular ejection fraction	63 (58-68)*
Coronary artery disease	136 (8.0)
Hypertension	1242 (72.7)
Diabetes mellitus	61 (3.6)
Chronic kidney disease	39 (2.3)
Marfan syndrome	52 (3.0)
Pericardial tamponade	16 (0.9)
Acute heart failure	12 (0.7)
Coma	3 (0.2)
Lower-limb malperfusion	154 (9.0)
Tracheotomy	5 (0.3)
CRRT	7 (0.4)
Previous stroke	59 (3.5)
Redo sternotomy	141 (8.3)
Cannulation site	
Right axillary artery	1349 (79.0)
Innominate artery	359 (21.0)
Main surgical procedure	
Hemiarch replacement	251 (14.7)
Total arch replacement	38 (2.2)
Frozen elephant trunk and total arch replacement	1419 (83.1)
Concomitant procedures	
Ascending aorta replacement	849 (49.7)
Bentall	637 (37.3)
CABG	105 (6.1)
Valve surgery	62 (3.6)

(Continued)

TABLE 1. Continued

Name	Total N = 1708
Extra-anatomic bypass	119 (7.0)
Ascending aorta other arteries	42
Left common carotid other arteries	37
Left subclavian other arteries	24
Bilateral femoral arteries	10
Innominate other arteries	3
Bilateral axillary arteries	3
Nasopharyngeal temperature (°C)	23.2 (22.0-24.2)
Rectal temperature (°C)	25.5 (24.2-26.8)†
Flow (mL/kg/min)	5.9 ± 1.8
Times	
Unilateral antegrade cerebral perfusion time (min)	37 (29-46)
Crossclamp time (min)	97 (78-123)
CPB time (min)	181 (155-212)
LBCA time (min)	24 (19-31)
Rewarming time (min)	81 (68-100)

Data presented as mean ± standard deviation or median and interquartile range (25%, quartile 1 to 75%, quartile 3) for continuous variables and n (%) for categorical variables. NYHA, New York Heart Association; CRRT, continuous renal replacement therapy; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest. *Available for 1657 patients. †Available for 1696 patients.

paraplegia during hospitalization. Stroke was defined as the presence of permanent neurologic deficits that consisted of abnormal movement of limbs, coma, epilepsy, and sensory loss affecting one side of the body, with confirmation of the diagnosis by a neurologist or correlation of the clinical diagnosis with morphologic changes revealed by neuroimaging examination. If patients had relevant neurologic dysfunction before surgery, stroke was defined as any newly developed sensorimotor deficit persisting at the time of discharge confirmed by neurologic consultations and neuroimaging examinations.^{3,7} Paraplegia was defined as numbness, weakness, or bilateral sensory dysfunction of the lower extremities that did not heal until hospital discharge. Patients who received preoperative CRRT were excluded from the assessment of postoperative CRRT data.

Unilateral antegrade cerebral perfusion time was defined as the period from the initiation of unilateral antegrade cerebral perfusion to bilateral antegrade cerebral perfusion. LBCA time was defined as the period from the initiation of LBCA to the restoration of distal aortic perfusion.

Statistical Analysis

Continuous variables were presented as median (interquartile range). Categorical variables were described as frequencies (%). Missing data are shown in Table 1. Random Forest imputation was used to maximize use of available data (details in Appendix E1).

Risk factors for outcomes were identified by univariate and multivariable logistic regression analyses with SPSS for Windows version 22.0 (SPSS, Chicago, Ill). All clinically relevant variables with *P* less than .100 on univariate analysis except for main surgical procedure were incorporated into the multivariable logistic models directly because of the obvious collinearity between main surgical procedure and DeBakey type. The tests for collinearity of variables and the accuracy of models are shown in Tables E1 to E6.

We used random Forest regression (RFR) with R software 3.5.1 (www.r-project.org) as the analytic strategy in part to avoid restrictive parametric modeling assumptions, given no prior knowledge of what relationships might exist, and in part because some studies previously demonstrated

with this method that there is a complex interplay between characteristics of diseases and outcomes (details in [Appendix E1](#)). Briefly, a random Forest is a collection of decision-tree analyses, wherein a variable is chosen to optimally split the population to improve prediction. This process is applied recursively to create a tree (recursive partitioning, classification, and regression trees). Individual trees “grown” by this method are inherently unstable, which can be mitigated by creating a collection of trees from bootstrap samples of the original data set. Subsequently, an ensemble average can be formulated across this Forest of individual trees. Validity of the Forest is evaluated by assessing outcomes of patients who were not selected in the bootstrap process (37%), resulting in internal multifold cross validation. This transforms variables associated with an outcome of interest into predictors of that outcome.

A random Forest was constructed with 1500 trees by the “randomForest” package. At each node, all variables (the day of operation, sex, age, body mass index, pathological DeBakey type, New York Heart Association [NYHA] score, left ventricular ejection fraction, coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, Marfan syndrome, pericardial tamponade, acute heart failure, coma, lower-limb malperfusion, tracheotomy, previous CRRT, previous stroke, redo sternotomy, cannulation site of unilateral antegrade cerebral perfusion, main surgery procedure, ascending aorta replacement, Bentall, coronary artery bypass grafting [CABG], valve surgery, extra-anatomic bypass, nasopharyngeal temperature, rectal temperature, cerebral perfusion flow, unilateral antegrade cerebral perfusion time, crossclamp time, CPB, LBCA time, and rewarming time) were used, but 6 candidate variables were randomly selected from among these for splitting each node.

The variable importance was measured by the Gini index (details in [Appendix E1](#)). We used partial dependence to determine how variables were related to outcomes. Partial dependency adjusted for all variables in the model. Conditional partial dependence plots were used to detect interactions between the variables (LBCA time, unilateral antegrade cerebral perfusion time, and nasopharyngeal temperature) and the outcomes.⁸

RESULTS

Demographic Characteristics

A total of 1708 patients who underwent aortic arch surgery with definite hypothermic circulatory arrest and unilateral antegrade cerebral perfusion over the 7-year observation period were selected for this study. The demographic characteristics are listed in [Table 1](#). The mean age of all patients was 47 years. Three-quarters of the patients were men. The aortic diseases affecting the patients were aortic dissection (90.6%), aortic aneurysm (7.9%), and pseudoaneurysm (1.5%). In patients with aortic dissection, acute aortic dissection accounted for 57.8%, subacute aortic dissection accounted for 17.6%, and chronic aortic dissection accounted for 24.6% of the cases. DeBakey type I and II dissections accounted for 86.6% and 13.4% of dissection cases, respectively. Marfan syndrome was diagnosed in 3.0% of patients. A history of hypertension was reported in 72.7% of patients.

Thirty-Day Mortality and Morbidity

Thirty-day mortality was 6.1% (n = 104). The incidence of permanent neurologic dysfunction was 4.8% (n = 82). The incidences of stroke and paraplegia were 2.8% (n = 48) and 2.0% (n = 34), respectively. The incidence of acute renal dysfunction requiring CRRT was 7.9%

TABLE 2. Early outcomes of all patients

Name	N = 1708
30-d death	104 (6.1)
In-hospital death	112 (6.6)
Intraoperative death	2
Permanent neurologic dysfunction	43
Circulatory failure	34
Ventricular arrhythmia	8
Infection	7
Hepatic failure	4
Renal failure	4
Distal aneurysm rupture	4
Respiratory failure	4
Gastrointestinal hemorrhage	1
Lower osteofascial compartment syndrome	1
Permanent neurologic dysfunction	82 (4.8)
Stroke/coma	48 (2.8)
Paraplegia	34 (2.0)
CRRT	135 (7.9)
Infection	45 (2.7)
Atrial fibrillation	211 (12.4)
Ventricular fibrillation	22 (1.3)
Cardiac arrest	13 (0.8)
Intra-aortic balloon pump	3 (0.2)
Extracorporeal membrane oxygenation	10 (0.6)
Left heart bypass	3 (0.2)
Tracheotomy	64 (3.7)
Reexploration for bleeding	102 (6.0)
Mechanical ventilation time (h)	18 (14-43)
Intensive care unit stay time (d)	2 (1-3)

Data presented as median and interquartile range (25%, quartile 1 to 75%, quartile 3) for continuous variables and n (%) for categorical variables. CRRT, Continuous renal replacement therapy.

(n = 135). In-hospital death and other postoperative complications are listed in [Table 2](#).

Risk Factors for 30-Day Mortality

In multivariable logistic analysis, age (odds ratio [OR], 1.03; $P = .010$), DeBakey type I dissection (OR, 3.26; $P = .009$), NYHA score (OR, 2.28; $P < .001$), coma (OR, 25.99; $P = .012$), CABG (OR, 2.99; $P = .002$), extra-anatomic bypass (OR, 4.48; $P < .001$), and CPB time (OR, 1.01; $P < .001$) were independent risk factors for 30-day mortality ([Table 3](#)).

Risk Factors for Permanent Neurologic Dysfunction

In multivariable logistic analysis, age (OR, 1.04; $P = .001$), DeBakey type I dissection (OR, 4.74; $P = .005$), and CPB time (OR, 1.01; $P = .014$) were independent risk factors for permanent neurologic dysfunction ([Table 4](#)).

TABLE 3. Univariate and multivariable logistic regression analyses of 30-day mortality for all patients

Name	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Day of operation (d)	1.00 (1.00-1.00)	.669		
Sex (male)	1.26 (0.77-2.04)	.358		
Age (y)	1.02 (1.00-1.04)	.020	1.03 (1.01-1.05)	.010
BMI (kg/m ²)	1.01 (0.95-1.06)	.853		
Acute aortic dissection	1.71 (1.13-2.58)	.011	1.12 (0.69-1.83)	.646
DeBakey (I)	3.88 (1.79-8.44)	.001	3.26 (1.35-7.87)	.009
NYHA	2.37 (1.68-3.35)	<.001	2.28 (1.57-3.32)	<.001
LVEF	0.98 (0.96-1.01)	.197		
Coronary artery disease	1.72 (0.94-3.16)	.081	0.75 (0.34-1.65)	.475
Hypertension	1.20 (0.75-1.90)	.444		
Diabetes mellitus	1.08 (0.39-3.05)	.876		
Chronic kidney disease	2.92 (1.19-7.12)	.019	1.54 (0.48-4.88)	.466
Pericardial tamponade	3.64 (1.02-12.96)	.047	1.53 (0.27-8.70)	.634
Acute heart failure	1.41 (0.18-11.00)	.745		
Coma	7.77 (0.70-86.47)	.095	25.99 (2.07-326.37)	.012
Lower-limb malperfusion	1.10 (0.55-2.12)	.826		
Tracheotomy	3.88 (0.43-35.06)	.227		
CRRT	6.27 (1.20-32.72)	.029	4.34 (0.54-35.05)	.169
Previous stroke	1.13 (0.40-3.17)	.821		
Redo sternotomy	1.49 (0.80-2.79)	.212		
Cannulation site				
Right axillary artery	0.79 (0.50-1.25)	.305		
Innominate artery	1.27 (0.80-2.02)	.305		
Main surgical procedure*		.044	—	—
Hemiarch replacement	0.40 (0.18-0.86)	.020		
TAR	0.37 (0.05-2.74)	.332		
FET and TAR	—	—		
Concomitant procedures				
Ascending aorta replacement	1.19 (0.80-1.78)	.384		
Bentall	1.10 (0.73-1.65)	.643		
CABG	4.26 (2.49-7.26)	<.001	2.99 (1.48-6.06)	.002
Valve surgery	1.69 (0.71-4.03)	.234		
Extra-anatomic bypass	2.02 (1.09-3.73)	.025	4.48 (2.13-9.42)	<.001
Nasopharyngeal temperature (°C)	0.88 (0.80-0.98)	.018	0.95 (0.82-1.10)	.515
Rectal temperature (°C)	0.87 (0.80-0.95)	.003	0.96 (0.84-1.09)	.511
Flow (mL/kg/min)	0.97 (0.87-1.09)	.623		
Times				
UACP time (min)	1.03 (1.02-1.04)	<.001	1.01 (0.99-1.03)	.307
Crossclamp time (min)	1.01 (1.01-1.02)	<.001	1.00 (0.99-1.01)	.729
CPB time (min)	1.01 (1.01-1.02)	<.001	1.01 (1.01-1.01)	<.001
LBCA time (min)	1.01 (0.99-1.03)	.105		
Rewarming time (min)	1.02 (1.01-1.02)	<.001	1.00 (0.99-1.01)	.947

OR, Odds ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CRRT, continuous renal replacement therapy; TAR, total arch replacement; FET, frozen elephant trunk; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest. *Main surgical procedure was removed from the final multivariable model because of the collinearity between main surgical procedure and DeBakey type.

TABLE 4. Univariate and multivariable logistic regression analyses of permanent neurologic dysfunction for all patients

Name	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Day of operation (d)	1.00 (1.00-1.00)	.038	1.00 (1.00-1.00)	.080
Sex (male)	1.11 (0.66-1.87)	.704		
Age (y)	1.04 (1.02-1.06)	.001	1.04 (1.02-1.06)	.001
BMI (kg/m ²)	1.01 (0.95-1.07)	.853		
Acute aortic dissection	1.81 (1.13-2.89)	.013	1.07 (0.63-1.80)	.800
DeBakey (I)	5.43 (1.97-14.93)	.001	4.74 (1.62-13.90)	.005
NYHA	1.52 (1.05-2.19)	.027	1.25 (0.85-1.85)	.260
LVEF	0.99 (0.96-1.02)	.470		
Coronary artery disease	1.65 (0.83-3.28)	.151		
Hypertension	1.71 (0.97-3.03)	.064	1.23 (0.67-2.24)	.509
Diabetes mellitus	1.03 (0.32-3.35)	.965		
Chronic kidney disease	1.07 (0.25-4.53)	.923		
Lower limb malperfusion	1.26 (0.62-2.57)	.526		
Tracheotomy	5.01 (0.55-45.30)	.152		
Previous stroke	2.34 (0.98-5.62)	.056	2.04 (0.80-5.18)	.133
Redo sternotomy	0.71 (0.28-1.79)	.469		
Cannulation site				
Right axillary artery	0.57 (0.30-1.08)	.084	1.41 (0.72-2.75)	.316
Innominate artery	1.76 (0.92-3.35)	.087		
Main surgical procedure*		.023	—	—
Hemiarch replacement	0.14 (0.03-0.57)	.006		
TAR	0.96 (0.23-4.04)	.950		
FET and TAR	—	—		
Concomitant procedures				
Ascending aorta replacement	1.45 (0.93-2.28)	.103		
Bentall	0.82 (0.51-1.31)	.403		
CABG	2.83 (1.48-5.40)	.002	1.95 (0.93-4.07)	.077
Valve surgery	0.65 (0.16-2.72)	.557		
Extra-anatomic bypass	0.86 (0.34-2.17)	.751		
Nasopharyngeal temperature (°C)	0.91 (0.81-1.02)	.096	0.89 (0.76-1.05)	.181
Rectal temperature (°C)	0.90 (0.82-1.00)	.044	0.97 (0.85-1.12)	.686
Flow (mL/kg/min)	0.97 (0.85-1.10)	.600		
Times				
UACP time (min)	1.01 (1.00-1.03)	.048	1.00 (0.98-1.02)	.853
Crossclamp time (min)	1.01 (1.00-1.01)	<.001	1.00 (0.99-1.01)	.305
CPB time (min)	1.01 (1.01-1.01)	<.001	1.01 (1.00-1.01)	.014
LBCA time (min)	0.99 (0.97-1.01)	.450		
Rewarming time (min)	1.01 (1.00-1.02)	.002	1.00 (0.99-1.01)	.594

OR, Odds ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TAR, total arch replacement; FET, frozen elephant trunk; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest. *Main surgical procedures were removed from the final multivariable model because of the collinearity between main surgical procedure and DeBakey type.

Risk Factors for Paraplegia

In multivariable logistic analysis, age (OR, 1.04; $P = .030$) and DeBakey type I dissection (OR, 4.72; $P = .039$) were independent risk factors for paraplegia (Table 5).

Risk Factors for Acute Renal Dysfunction Requiring Continuous Renal Replacement Therapy

In multivariable logistic analysis, the day of operation (OR, 1.001; $P = .007$), age (OR, 1.03; $P < .001$), previous chronic kidney disease (OR, 7.82; $P < .001$), valve surgery

TABLE 5. Univariate and multivariable logistic regression analyses of paraplegia for all patients

Name	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Day of operation (d)	1.00 (1.00-1.00)	.346		
Sex (male)	1.08 (0.49-2.41)	.848		
Age (y)	1.04 (1.01-1.07)	.025	1.04 (1.00-1.07)	.030
BMI (kg/m ²)	0.96 (0.87-1.05)	.371		
Acute aortic dissection	1.31 (0.66-2.61)	.442		
DeBakey (I)	4.32 (1.03-18.12)	.045	4.72 (1.08-20.58)	.039
NYHA	1.01 (0.58-1.75)	.975		
LVEF	0.97 (0.93-1.02)	.206		
Coronary artery disease	3.11 (1.33-7.27)	.009	1.72 (0.63-4.68)	.292
Hypertension	2.20 (0.85-5.73)	.105		
Diabetes mellitus	1.71 (0.40-7.31)	.469		
Lower-limb malperfusion	1.77 (0.67-4.63)	.248		
Previous stroke	0.84 (0.11-6.28)	.869		
Cannulation site				
Right axillary artery	2.02 (0.71-5.77)	.190		
Innominate artery	0.50 (0.17-1.42)	.190		
Main surgical procedure		.222		
Hemiarch replacement	0.17 (0.02-1.28)	.085		
TAR	1.17 (0.16-8.80)	.878		
FET and TAR	—	—		
Concomitant procedures				
Ascending aorta replacement	1.65 (0.82-3.32)	.160		
Bentall	0.80 (0.39-1.65)	.548		
CABG	4.17 (1.77-9.81)	.001	2.64 (0.95-7.30)	.062
Valve surgery	1.68 (0.39-7.18)	.483		
Extra-anatomic bypass	1.30 (0.39-4.32)	.668		
Nasopharyngeal temperature (°C)	0.98 (0.81-1.17)	.794		
Rectal temperature (°C)	0.98 (0.84-1.14)	.755		
Flow (mL/kg/min)	0.96 (0.79-1.18)	.700		
Times				
UACP time (min)	1.00 (0.98-1.03)	.986		
Crossclamp time (min)	1.01 (1.00-1.01)	.063	1.00 (0.99-1.01)	.861
CPB time (min)	1.01 (1.00-1.01)	.019	1.00 (0.99-1.01)	.976
LBCA time (min)	0.98 (0.94-1.01)	.178		
Rewarming time (min)	1.01 (1.00-1.02)	.019	1.00 (0.99-1.02)	.501

OR, Odds ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TAR, total arch replacement; FET, frozen elephant trunk; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest.

(OR, 2.78; $P = .015$), and CPB time (OR, 1.01; $P = .001$) were independent risk factors for CRRT (Table 6).

Unilateral Antegrade Cerebral Perfusion Time

In RFR, the variable importance is shown in Figure E1. We further analyzed associations of the unilateral antegrade cerebral perfusion time with the outcomes. When unilateral antegrade cerebral perfusion time was more than 38 minutes, an upward trend was observed in 30-day mortality. At the

beginning, this trend was steep from 38 to 43 minutes and stayed at this level until 58 minutes. Then this trend became sharp again. Likewise, an upward trend was observed for permanent neurologic dysfunction when unilateral antegrade cerebral perfusion time was more than 38 minutes (Figure 1).

Lower-Body Circulatory Arrest Time

In the RFR, a sharp upward trend for paraplegia was observed when LBCA time was more than 40 minutes

TABLE 6. Univariate and multivariable logistic regression analyses of continuous renal replacement therapy for all patients who underwent aortic arch surgery with hypothermic circulatory arrest and unilateral antegrade cerebral perfusion without previous continuous renal replacement therapy

Name	Univariate		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Day of operation (d)	1.00 (1.00-1.01)	<.001	1.00 (1.000-1.001)	.007
Sex (male)	0.95 (0.63-1.42)	.796		
Age (y)	1.03 (1.02-1.05)	<.001	1.03 (1.02-1.05)	<.001
BMI (kg/m ²)	1.01 (0.97-1.06)	.566		
Acute aortic dissection	2.14 (1.47-3.12)	<.001	1.30 (0.82-2.07)	.269
DeBakey (I)	2.89 (1.58-5.29)	.001	1.77 (0.88-3.57)	.112
NYHA	1.51 (1.13-2.03)	.006	1.12 (0.81-1.54)	.513
LVEF	1.02 (0.99-1.04)	.234		
Coronary artery disease	1.56 (0.88-2.76)	.125		
Hypertension	1.83 (1.15-2.91)	.010	1.35 (0.80-2.28)	.270
Diabetes mellitus	1.32 (0.56-3.13)	.527		
Chronic kidney disease	10.54 (5.22-21.29)	<.001	7.82 (3.57-17.11)	<.001
Marfan syndrome	0.73 (0.22-2.36)	.596		
Pericardial tamponade	4.91 (1.52-15.87)	.008	1.32 (0.30-5.92)	.714
Coma	6.02 (0.54-66.87)	.144		
Lower-limb malperfusion	2.06 (1.25-3.39)	.005	1.68 (0.97-2.91)	.067
Tracheotomy	3.01 (0.33-27.11)	.326		
Previous stroke	1.11 (0.44-2.83)	.823		
Redo sternotomy	1.01 (0.53-1.93)	.966		
Cannulation site				
Right axillary artery	1.02 (0.66-1.58)	.934		
Innominate artery	0.98 (0.63-1.53)	.934		
Main surgical procedure*		.028	—	—
Hemiarch replacement	0.40 (0.20-0.80)	.009		
TAR	0.60 (0.14-2.51)	.482		
FET and TAR	—	—		
Concomitant procedures				
Ascending aorta replacement	1.39 (0.97-2.00)	.074	1.20 (0.79-3.02)	.205
Bentall	1.08 (0.75-1.56)	.669		
CABG	2.54 (1.46-4.42)	.001	1.54 (0.79-3.02)	.205
Valve surgery	2.46 (1.22-4.96)	.012	2.78 (1.22-6.30)	.015
Extra-anatomic bypass	1.24 (0.65-2.37)	.516		
Nasopharyngeal temperature (°C)	0.95 (0.87-1.04)	.263		
Rectal temperature (°C)	0.92 (0.85-0.99)	.032	0.93 (0.83-1.03)	.137
Flow (mL/kg/min)	0.94 (0.85-1.05)	.292		
Times				
UACP time (min)	1.02 (1.01-1.03)	<.001	1.00 (0.97-1.02)	.906
Crossclamp time (min)	1.02 (1.01-1.02)	<.001	1.00 (0.99-1.01)	.947
CPB time (min)	1.01 (1.01-1.02)	<.001	1.01 (1.01-1.02)	<.001
LBCA time (min)	1.02 (1.01-1.03)	.008	1.00 (0.98-1.03)	.925
Rewarming time (min)	1.01 (1.01-1.02)	<.001	1.00 (0.99-1.00)	.147

OR, Odds ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; TAR, total arch replacement; FET, frozen elephant trunk; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest. *Main surgical procedures were removed from the final multivariable model because of the collinearity between main surgical procedure and DeBakey type.

FIGURE 1. Probability for early outcomes with prolonged unilateral antegrade cerebral perfusion times. A, Probability for 30-day mortality with prolonged unilateral antegrade cerebral perfusion times. An upward trend was steep from 38 to 43 minutes and stayed at this level until 58 minutes. Then this trend became sharp again. B, Probability for permanent neurologic dysfunction with prolonged unilateral antegrade cerebral perfusion times. An upward trend was observed when unilateral antegrade cerebral perfusion time was more than 38 minutes. The blue areas are from 2.5% to 97.5%, representing 95% of the patients. P_{2.5}, 2.5th percentile; P_{97.5}, 97.5th percentile.

(Figure 2, C). No obvious trends for 30-day mortality and CRRT were observed from 12 minutes (the 2.5th percentile) to 54 minutes (the 97.5th percentile) (Figure 2, A and B).

Nasopharyngeal Temperature

In the RFR, a slow downward trend was observed in 30-day mortality when nasopharyngeal temperature was lower than 24.3°C. However, when the temperature was higher than 25.0°C, a sharp upward trend began to appear (Figure 3, A). Likewise, a slow downward trend for permanent neurologic dysfunction was observed before 24.0°C and then a sharp upward trend began to appear (Figure 3, B). A slow downward trend for CRRT was observed before 24.3°C, and then a sharp upward trend began to appear (Figure 3, C). A downward trend for paraplegia was observed before 22.3°C, and a steep upward trend was observed after 24.0°C, with slight fluctuations (Figure 3, D).

DISCUSSION

In conducting the present retrospective study, we analyzed data from the largest reported cohort of patients

who have undergone aortic arch surgery with definite hypothermic circulatory arrest and unilateral antegrade cerebral perfusion, including clinical status, demographic data, surgical procedures, circulatory management strategies, cerebral protection strategies, and clinical outcomes (30-day mortality, the incidence of permanent neurologic dysfunction, and the use rate of CRRT) associated with these surgical procedures. The results showed that advanced age, DeBakey type I dissection, poor cardiac function, preoperative coma, CABG, extra-anatomic bypass, and prolonged CPB time were independent risk factors for 30-day mortality. Advanced age, DeBakey type I dissection, and prolonged CPB time were independent risk factors for permanent neurologic dysfunction. The day of operation, advanced age, previous chronic renal dysfunction, valve surgery, and prolonged CPB time were independent risk factors for CRRT. Additionally, the results of the RFR analyses showed that the risk for 30-day mortality and permanent neurologic dysfunction began to increase when unilateral antegrade cerebral perfusion time was longer than 38 minutes. The risk for

FIGURE 2. Probability for early outcomes with prolonged LBCA times. A, Probability for 30-day mortality with prolonged LBCA times. No obvious trend was observed in 95% of patients. B, Probability for acute renal dysfunction requiring CRRT with prolonged LBCA times. No obvious trend was observed in 95% of patients. C, Probability for paraplegia with prolonged LBCA times. A sharp upward trend was observed when LBCA time was longer than 40 minutes. The blue areas are from 2.5% to 97.5%, representing 95% of the patients. *P*_{2.5}, 2.5th percentile; *P*_{97.5}, 97.5th percentile; CRRT, continuous renal replacement therapy.

permanent neurologic dysfunction, CRRT, and paraplegia increased when the temperature was higher than approximately 24°C.

The etiology of aortic disease and patient demographics in our study varied significantly from other studies. The mean age of all patients was lower, and the proportion of male patients was higher.⁴ Only 7.9% of patients experienced an aortic aneurysm, and most of them had an aortic dissection. The proportion of patients presenting with aortic aneurysm was significantly lower than the percentage in

other studies.⁹ These results might be attributed to different racial backgrounds, high incidence of hypertension, and low rates of hypertension control^{10,11} in China. Although the patients in our study were younger, the proportion of patients with hypertension was similar to the percentage reported in other studies.¹²⁻¹⁴ The percentage of patients diagnosed with Marfan syndrome (3%) was lower than reported in other studies.^{15,16} The incidences of coronary artery disease, diabetes, and renal failure were lower, which might be due to the lower mean age.^{17,18}

FIGURE 3. Probability for early outcomes with increased nasopharyngeal temperatures. A, Probability for 30-day mortality with increased nasopharyngeal temperatures. A slow downward trend was observed before 24.3°C, and an upward trend was observed after 25.0°C. B, Probability for permanent neurologic dysfunction with increased nasopharyngeal temperatures. A slow downward trend was observed before 24.0°C, and an upward trend was observed after 24.0°C. C, Probability for acute renal dysfunction requiring CRRT with increased nasopharyngeal temperatures. A slow downward trend was observed before 24.3°C, and an upward trend was observed after 24.3°C. D, Probability for paraplegia with increased nasopharyngeal temperatures. A downward trend was observed before 22.3°C, and a steep upward trend was observed after 24.0°C, with slight fluctuations. The blue areas are from 2.5% to 97.5%, representing 95% of the patients. P_{2.5}, 2.5th percentile; P_{97.5}, 97.5th percentile; CRRT, continuous renal replacement therapy.

Thirty-day mortality (6.1%) and the rate of permanent neurologic dysfunction (4.8%) in our study were comparable with the rates observed in other case series reported in the literature (mortality, 8%-15.9%; rate of permanent neurologic dysfunction, 6%-10.5%).^{3,16-18} Similar to previous studies, in our study, the multivariable analysis identified advanced age,^{19,20} poor cardiac function,²¹ preoperative coma,²² CABG,²³ and prolonged CPB time^{21,24} as independent risk factors for mortality. Advanced age^{20,25} and prolonged CPB time^{21,24} were also independent risk factors for permanent neurologic dysfunction. Additionally, advanced age,^{19,23,24} preoperative chronic renal dysfunction,²⁶ and prolonged CPB time²² were independent risk factors for CRRT.

The reported incidence of paraplegia in patients who underwent frozen elephant trunk appeared to be significantly higher than in those who were treated with the conventional elephant trunk procedure (7.5%-21.7% vs 1.8%-5.6%).²⁷⁻³⁰ In the present retrospective study, most of the patients underwent frozen elephant trunk and total arch replacement, but the incidence of paraplegia (2.0%) was lower than in other case series focusing on frozen elephant trunk reported in the literature. We did not find that frozen elephant trunk and total arch replacement increased the risk for paraplegia in traditional logistic regression and RFR analyses, unlike the study by Leontyev and colleagues.²⁹ One factor that differed from other studies discussing frozen elephant trunk procedures was the LBCA time, which was significantly shorter in the present retrospective study. Roselli and colleagues³¹ reported no cases of paraplegia in their series of 17 patients who underwent frozen elephant trunk procedures, with an average LBCA time comparable to the time reported in the present retrospective study. Some studies have raised concerns about the safety of the spinal cord in relation to LBCA. This study also found that the risk for paraplegia increased when LBCA time was longer than 40 minutes. Thus, the lower incidence of paraplegia could be explained by the shorter LBCA time in our center, a consequence of the unique surgical procedure we have implemented.

A large number of existing studies^{3,17,19,23} suggested that LBCA time had a significant effect on short-term mortality or permanent neurologic dysfunction. However, we did not observe a similar effect in traditional logistic regression and RFR analyses. Several factors could explain the difference in findings. Previous studies³ had more confounding factors because they were multicenter studies or involved multiple surgical teams. Our analysis consists of a single-center study, involving surgical procedures performed by the same surgical team. In addition, the LBCA time was significantly shorter and had smaller individual differences across the cohort in this study than in previous studies^{18,19} because of the surgical protocol of our center. Most of the LBCA times were within the safe time limit reported previously^{3,32} and did

not have an impact on prognosis. Most patients who underwent prolonged LBCA were in low numbers and scattered throughout the cohort.

In addition to the effects of LBCA time, previous studies^{3,24,25} have reported that prognosis was significantly influenced by the unilateral antegrade cerebral perfusion time. In our study, the RFR analysis showed there is a safety threshold (38 minutes) of unilateral antegrade cerebral perfusion time in relation to 30-day mortality and permanent neurologic dysfunction. Thus, we consider unilateral antegrade cerebral perfusion time an important predictor for short-term adverse outcomes during aortic arch surgery, especially when longer than 38 minutes. However, the causes of this result remain unclear. In-depth studies should further explore the mechanisms underlying the relationship between unilateral antegrade cerebral perfusion duration and adverse events.

In recent years, research has focused on temperature management strategies during LBCA. Like previous studies^{24,33} that found benefits to higher temperature management strategies, our study confirmed that an increase in temperature during LBCA was related to a decrease in 30-day mortality or in incidence of permanent neurologic dysfunction in the RFR analysis. This may be related to a reduction in CPB times, postoperative bleeding, endothelial dysfunction, neuronal apoptosis, and postoperative pulmonary complications, which are typically associated with deep hypothermia.^{9,17,18,34} However, the benefit was demonstrated only below the safety threshold for temperature ($\sim 24^{\circ}\text{C}$), because the risks for permanent neurologic dysfunction, paraplegia, and acute renal dysfunction requiring CRRT increased with temperatures above the safety threshold. Other studies^{14,24,32} have reported that higher temperature circulatory management may carry a risk of spinal cord and visceral ischemia in patients undergoing prolonged LBCA. Our study confirmed that higher nasopharyngeal temperature ($>24^{\circ}\text{C}$) correlates with a higher incidence of postoperative paraplegia and acute renal dysfunction requiring CRRT in the RFR analyses. However, larger-scale, multicenter studies are necessary to confirm these results and to clarify whether the increased risk associated with higher nasopharyngeal temperature occurs only in patients who undergo prolonged LBCA.

Study Limitations

Our study had several limitations. First, this study was subject to the limitations inherent to any retrospective, observational study from a single center, such as missing data, bias due to memory errors, and lack of representativeness. Some of the necessary variables were not found in the retrospective database. Second, a previous study has pointed out that neurologic evaluation is inadequate in retrospective studies.³⁵ In this study, permanent neurologic

dysfunction might be underestimated because neurologic evaluations and neuroimaging were not performed in patients in whom the neurologist did not observe symptoms suggestive of postoperative stroke or paraplegia. Third, in our center, LBCA time was shorter and individual differences in LBCA time were smaller compared with other studies. Moreover, most of the LBCA times were within the safe time limit reported previously.^{3,32} Shorter LBCA duration might explain the lack of correlation between LBCA time and 30-day mortality or CRRT. Fourth, although this study included a large sample, some critical cases might have been excluded. In cases of acute type A aortic dissection, the median time from onset to diagnosis was 2 (1-4) days. The rate of surgical intervention within 24 hours was also lower than the rate reported in other studies.³ Our center is the largest referral center for aortic disease in China. In some cases, timely treatment was impossible because of delayed transportation to our hospital. Finally, although acute, subacute, and chronic aortic dissection accounted for most cases, the causes of aortic arch surgery were heterogeneous throughout the cohort. However, we performed sensitivity analyses to explore the effects of different pathological types on outcomes.

CONCLUSIONS

In this single-center study, we reported the clinical experience associated with aortic arch surgery, including patient demographics, surgical procedures, circulatory management strategies, cerebral protection strategies, and clinical outcomes over the span of 7 years. When used as a cerebral protection strategy, unilateral antegrade cerebral perfusion may have a safety threshold of 38 minutes in relation to 30-day mortality and permanent neurologic dysfunction. Moderate hypothermia proved to be a safe and effective circulatory management strategy. However, temperatures greater than approximately 24°C should be used cautiously to minimize the risk for postoperative permanent neurologic dysfunction, paraplegia, and acute renal dysfunction requiring CRRT.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

The authors thank Wei Pan, who provided advice on the structure of the manuscript.

References

1. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2873-926.
2. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283:897-903.
3. Kruger T, Weigang E, Hoffmann I, Blettner M, Aebert H. Cerebral protection during surgery for acute aortic dissection type A: results of the German Registry for Acute Aortic Dissection Type A (GERAADA). *Circulation*. 2011;124:434-43.
4. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350-8.
5. Sun L, Qi R, Zhu J, Liu Y, Zheng J. Total arch replacement combined with stented elephant trunk implantation: a new "standard" therapy for type A dissection involving repair of the aortic arch? *Circulation*. 2011;123:971-8.
6. Ma WG, Zhu JM, Zheng J, Liu YM, Ziganshin BA, Elefteriades JA, et al. Sun's procedure for complex aortic arch repair: total arch replacement using a tetrafurcate graft with stented elephant trunk implantation. *Ann Cardiothorac Surg*. 2013;2:642-8.
7. Bossone E, Corteville DC, Harris KM, Suzuki T, Fattori R, Hutchison S, et al. Stroke and outcomes in patients with acute type A aortic dissection. *Circulation*. 2013;128(11 Suppl 1):S175-9.
8. Raja S, Rice TW, Ehrlinger J, Goldblum JR, Rybicki LA, Murthy SC, et al. Importance of residual primary cancer after induction therapy for esophageal adenocarcinoma. *J Thorac Cardiovasc Surg*. 2016;152:756-61.e5.
9. Leshnower BG, Myung RJ, Kilgo PD, Vassiliades TA, Vega JD, Thourani VH, et al. Moderate hypothermia and unilateral selective antegrade cerebral perfusion: a contemporary cerebral protection strategy for aortic arch surgery. *Ann Thorac Surg*. 2010;90:547-54.
10. Czerny M, Krahenbuhl E, Reineke D, Sodeck G, Englberger L, Weber A, et al. Mortality and neurologic injury after surgical repair with hypothermic circulatory arrest in acute and chronic proximal thoracic aortic pathology: effect of age on outcome. *Circulation*. 2011;124:1407-13.
11. Peacock E, Krousel-Wood M. Adherence to antihypertensive therapy. *Med Clin North Am*. 2017;101:229-45.
12. Ergin MA, Galla JD, Lansman SL, Quintana C, Bodian C, Griep 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.
13. Liu H, Chang Q, Zhang H, Yu C. Predictors of adverse outcome and transient neurological dysfunction following aortic arch replacement in 626 consecutive patients in China. *Heart Lung Circ*. 2017;26:172-8.
14. Pacini D, Pantaleo A, Di Marco L, Leone A, Barberio G, Murana G, et al. Visceral organ protection in aortic arch surgery: safety of moderate hypothermia. *Eur J Cardiothorac Surg*. 2014;46:438-43.
15. Berretta P, Patel HJ, Gleason TG, Sundt TM, Myrmel T, Desai N, et al. IRAD experience on surgical type A acute dissection patients: results and predictors of mortality. *Ann Cardiothorac Surg*. 2016;5:346-51.
16. Zierer A, Detho F, Dzemali O, Aybek T, Moritz A, Bakhtiyar F. Antegrade cerebral perfusion with mild hypothermia for aortic arch replacement: single-center experience in 245 consecutive patients. *Ann Thorac Surg*. 2011;91:1868-73.
17. Comas GM, Leshnower BG, Halkos ME, Thourani VH, Puskas JD, Guyton RA, et al. Acute type A dissection: impact of antegrade cerebral perfusion under moderate hypothermia. *Ann Thorac Surg*. 2013;96:2135-41.
18. Leshnower BG, Thourani VH, Halkos ME, Sarin EL, Keeling WB, Lamias MJ, et al. Moderate versus deep hypothermia with unilateral selective antegrade cerebral perfusion for acute type A dissection. *Ann Thorac Surg*. 2015;100:1563-9.
19. Preventza O, Simpson KH, Cooley DA, Cornwell L, Bakaeen FG, Omer S, et al. Unilateral versus bilateral cerebral perfusion for acute type A aortic dissection. *Ann Thorac Surg*. 2015;99:80-7.
20. Safi HJ, Miller CC III, Lee TY, Estrera AL. Repair of ascending and transverse aortic arch. *J Thorac Cardiovasc Surg*. 2011;142:630-3.
21. Okada K, Omura A, Kano H, Sakamoto T, Tanaka A, Inoue T, et al. Recent advancements of total aortic arch replacement. *J Thorac Cardiovasc Surg*. 2012;144:139-45.
22. Numata S, Tsutsumi Y, Monta O, Yamazaki S, Seo H, Sugita R, et al. Aortic arch repair with antegrade selective cerebral perfusion using mild to moderate hypothermia of more than 28 degrees C. *Ann Thorac Surg*. 2012;94:90-6.
23. Zierer A, El-Sayed Ahmad A, Papadopoulos N, Moritz A, Diegeler A, Urbanski PP. Selective antegrade cerebral perfusion and mild (28 degrees C-30 degrees C) systemic hypothermic circulatory arrest for aortic arch replacement: results from 1002 patients. *J Thorac Cardiovasc Surg*. 2012;144:1042-9.
24. Kamiya H, Hagl C, Kropivnitskaya I, Bothig D, Kallenbach K, Khaladj N, et al. The safety of moderate hypothermic lower body circulatory arrest with selective cerebral perfusion: a propensity score analysis. *J Thorac Cardiovasc Surg*. 2007;133:501-9.

25. Preventza O, Garcia A, Tuluca A, Henry M, Cooley DA, Simpson K, et al. Innominate artery cannulation for proximal aortic surgery: outcomes and neurological events in 263 patients. *Eur J Cardiothorac Surg*. 2015;48:937-42.
26. Nota H, Asai T, Suzuki T, Kinoshita T, Ikegami H, Takashima N. Risk factors for acute kidney injury in aortic arch surgery with selective cerebral perfusion and mild hypothermic lower body circulatory arrest. *Interact Cardiovasc Thorac Surg*. 2014;19:955-61.
27. Di Eusanio M, Borger M, Petridis FD, Leontyev S, Pantaleo A, Moz M, et al. Conventional versus frozen elephant trunk surgery for extensive disease of the thoracic aorta. *J Cardiovasc Med (Hagerstown)*. 2014;15:803-9.
28. Etz CD, Plestis KA, Kari FA, Luehr M, Bodian CA, Spielvogel D, et al. Staged repair of thoracic and thoracoabdominal aortic aneurysms using the elephant trunk technique: a consecutive series of 215 first stage and 120 complete repairs. *Eur J Cardiothorac Surg*. 2008;34:605-15.
29. Leontyev S, Borger MA, Etz CD, Moz M, Seeburger J, Bakhtiary F, et al. Experience with the conventional and frozen elephant trunk techniques: a single-centre study. *Eur J Cardiothorac Surg*. 2013;44:1076-83.
30. Shrestha M, Martens A, Kruger H, Maeding I, Ius F, Fleissner F, et al. Total aortic arch replacement with the elephant trunk technique: single-centre 30-year results. *Eur J Cardiothorac Surg*. 2014;45:289-96.
31. Roselli EE, Rafael A, Soltesz EG, Canale L, Lytle BW. Simplified frozen elephant trunk repair for acute DeBakey type I dissection. *J Thorac Cardiovasc Surg*. 2013;145(3 Suppl):S197-201.
32. Luehr M, Bachet J, Mohr FW, Etz CD. Modern temperature management in aortic arch surgery: the dilemma of moderate hypothermia. *Eur J Cardiothorac Surg*. 2014;45:27-39.
33. Preventza O, Coselli JS, Garcia A, Kashyap S, Akvan S, Simpson KH, et al. Moderate hypothermia at warmer temperatures is safe in elective proximal and total arch surgery: results in 665 patients. *J Thorac Cardiovasc Surg*. 2017;153:1011-8.
34. Algarni KD, Yanagawa B, Rao V, Yau TM. Profound hypothermia compared with moderate hypothermia in repair of acute type A aortic dissection. *J Thorac Cardiovasc Surg*. 2014;148:2888-94.
35. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609-20.

Key Words: aortic arch surgery, cerebral protection strategy, unilateral antegrade cerebral perfusion

APPENDIX E1. PRINCIPLES AND DETAILS OF STATISTIC METHOD

Details of Missing Data Imputation

Missing data are shown in Table 1. Random Forest imputation was used to maximize use of available data. We imputed values in predictor data using proximity from the “randomForest” package. The algorithm starts by imputing missing values using the median. The randomForest is called with completed data. The proximity matrix from the randomForest is used to update the imputation of the missing values. For continuous predictors, the imputed value is the weights average of the nonmissing observations, where the weights are the proximities. For categorical predictors, the imputed value is the category with the largest average proximity. This process is iterated times.^{E1}

Principles and Details of Random Forest

We used RFR with R software as the analytic strategy in part to avoid restrictive parametric modeling assumptions, given no prior knowledge of what relationships might exist, and in part because some studies previously demonstrated with this method that there is a complex interplay between characteristics of diseases and outcomes. A random Forest is a collection of decision-tree analyses, wherein a variable is chosen to optimally split the population to improve prediction. This process is applied recursively to create a tree (recursive partitioning, classification, and regression trees). Individual trees “grown” by this method are inherently unstable, which can be mitigated by creating a collection of trees from bootstrap samples of the original data set (the bootstrap data set is formed by random sampling of patients with replacement until a data set of equal size is generated; some patients will be duplicated, and an average of 37% will not be sampled). Subsequently, an ensemble average can be formulated across this Forest of individual trees. Validity of the Forest is evaluated by assessing outcomes of patients who were not selected in the bootstrap process, resulting in internal multifold cross validation. This transforms variables associated with an outcome of interest into predictors of that outcome.

We have used “randomForest” package to perform random Forest. A random Forest was constructed with 1500 trees. At each node, all variables (the day of operation, sex, age, body mass index, pathological, DeBakey type,

NYHA score, left ventricular ejection fraction, coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, Marfan syndrome, pericardial tamponade, acute heart failure, coma, lower-limb malperfusion, tracheotomy, previous CRRT, previous stroke, redo sternotomy, cannulation site of unilateral antegrade cerebral perfusion, main surgery procedure, ascending aorta replacement, Bentall, CABG, valve surgery, extra-anatomic bypass, nasopharyngeal temperature, rectal temperature, cerebral perfusion flow, unilateral antegrade cerebral perfusion time, cross-clamp time, CPB, LBCA time, rewarming time) were used, but 6 candidate variables were randomly selected from among these for splitting each node (which avoids the statistical problem related to the order in which variables are incorporated into models). The reasons why we chose 1500 trees and 6 candidate variables were that the model maintained stable and the error was minimal at that moment, respectively.

The Variable Importance

We have used the “randomForest” package to measure the variable importance. The variable importance measure was the total decrease in node impurities from splitting on the variable, averaged over all trees. For classification, the node impurity is measured by the Gini index. For regression, it is measured by residual sum of squares.

Partial Dependence Plot

We used partial dependence to determine how variables were related to outcomes. Partial dependency adjusted for all variables in the model. Conditional partial dependence plots were used to detect interactions between variables (LBCA time, unilateral antegrade cerebral perfusion time, and nasopharyngeal temperature) and the outcomes (30-day mortality, permanent neurologic dysfunction, paraplegia, and acute renal dysfunction requiring CRRT). Partial dependence (logits/log odds) was calculated by randomForest package. Then we converted logit units to probability using the formula $P = 1/[1 + \exp(-z)]$. “z” is the logit units that we have plotted.

E-Reference

E1. Breiman L. Manual for setting up, using, and understanding Random Forest V4.0. Available at: https://www.stat.berkeley.edu/~breiman/Using_random_forests_v4.0.pdf. Accessed May 20, 2018.

FIGURE E1. The variable importance for outcomes. A, The variable importance for 30-day mortality. B, The variable importance for permanent neurologic dysfunction. C, The variable importance for acute renal dysfunction requiring CRRT. D, The variable importance for paraplegia. *CPB*, Cardiopulmonary bypass; *UACP*, unilateral antegrade cerebral perfusion; *LVEF*, left ventricular ejection fraction; *PND*, permanent neurologic dysfunction; *CRRT*, continuous renal replacement therapy.

TABLE E1. Test for collinearity of variables planned to be included in the multivariable model for 30-day mortality

Variables	Tolerance	VIF
Age (y)	0.94	1.07
Acute aortic dissection	0.82	1.21
DeBakey type	0.03	32.41
NYHA	0.97	1.03
Coronary artery disease	0.84	1.19
Chronic kidney disease	0.91	1.10
Pericardial tamponade	0.95	1.05
Coma	0.99	1.01
Previous CRRT	0.93	1.08
Main surgical procedure	0.03	32.89
CABG	0.80	1.25
Extra-anatomic bypass	0.84	1.19
Nasopharyngeal temperature	0.61	1.65
Rectal temperature	0.58	1.72
UACP time	0.64	1.56
Crossclamp time	0.31	3.18
CPB time	0.25	3.95
Rewarming time	0.48	2.09

VIF, Variance Inflation Factor; NYHA, New York Heart Association; CRRT, continuous renal replacement therapy; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass.

TABLE E2. Test for collinearity of variables planned to be included in the multivariable model for postoperative permanent neurologic dysfunction

Variables	Tolerance	VIF
Time (d)	0.71	1.40
Age (y)	0.91	1.09
Acute aortic dissection	0.82	1.21
DeBakey type	0.03	32.15
NYHA	0.94	1.06
Hypertension	0.90	1.11
Previous stroke	0.98	1.02
Cannulation site	0.96	1.04
Main surgical procedure	0.03	32.16
CABG	0.89	1.13
Nasopharyngeal temperature	0.53	1.90
Rectal temperature	0.58	1.73
UACP time	0.65	1.55
Crossclamp time	0.32	3.15
CPB time	0.26	3.93
Rewarming time	0.48	2.09

VIF, Variance Inflation Factor; NYHA, New York Heart Association; CABG, Coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass.

TABLE E3. Test for collinearity of variables planned to be included in the multivariable model for postoperative paraplegia

Variables	Tolerance	VIF
Age (y)	0.97	1.03
Coronary artery disease	0.84	1.20
CABG	0.81	1.23
Crossclamp time	0.39	2.59
CPB time	0.25	3.96
Rewarming time	0.50	2.02

VIF, Variance Inflation Factor; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

TABLE E4. Test for collinearity of variables planned to be included in the multivariable model for postoperative continuous renal replacement therapy

Variables	Tolerance	VIF
Time (d)	0.82	1.22
Age (y)	0.89	1.12
Acute aortic dissection	0.80	1.25
DeBakey type	0.03	32.25
NYHA	0.94	1.07
Hypertension	0.88	1.14
Chronic kidney disease	0.97	1.03
Pericardial tamponade	0.97	1.03
Lower-limb malperfusion	0.98	1.02
Main surgical procedure	0.03	32.42
Ascending aorta replacement	0.86	1.16
CABG	0.89	1.13
Valve surgery	0.93	1.07
Rectal temperature	0.81	1.24
UACP time	0.32	3.15
Crossclamp time	0.32	3.13
CPB time	0.27	3.76
LBCA time	0.37	2.68
Rewarming time	0.49	2.02

VIF, Variance Inflation Factor; NYHA, New York Heart Association; CABG, coronary artery bypass grafting; UACP, unilateral antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LBCA, lower-body circulatory arrest.

TABLE E5. Accuracy of multivariable logistic regression models

Name	Accuracy (%)	Hosmer–Lemeshow test	
		Chi-square	P
30-d mortality (%)	93.85	3.252	.918
Permanent neurologic dysfunction	95.14	6.436	.598
CRRT	92.18	8.802	.359
Paraplegia	98.01	5.966	.651

CRRT, Continuous renal replacement therapy.

TABLE E6. Accuracy of random Forest regression models

Name	OBB estimate of error rate (%)
30-d mortality (%)	6.03
Permanent neurologic dysfunction	4.80
CRRT	7.82
Paraplegia	1.99

OBB, Out-of-bag; CRRT, Continuous renal replacement therapy.