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Original Article

Optimal hypothermia conditions for cerebral perfusion in the surgical repair of acute aortic dissection: a single-center pilot clinical study

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Abstract: Hypothermia with selective antegrade cerebral perfusion (SACP) is effective for brain protection during surgical treatment of type A aortic dissection (AAD). Yet, the optimal hypothermic conditions have not been determined. This randomized controlled trial evaluated the relative clinical efficacy and safety of SACP with hypothermia of various depths, for patients undergoing surgery for AAD repair. Sixty-five patients with AAD who underwent repair of the total aortic arch with artificial stents were randomly and equally allocated to 5 groups according to cerebral perfusion hypothermic temperature and blood volume. Patients in groups A (16-18°C, 5 mL/kg), B (18-20°C, 10 mL/kg), and C (20-22°C, 15 mL/kg) were treated with deep hypothermia; those in groups D (22-24°C, 20 mL/kg) and E (24-26°C, 25 mL/kg) underwent moderate hypothermia. The perioperative and postoperative outcomes were evaluated, particularly rates of transient and permanent neurological dysfunctions. All patient groups were comparable regarding post-procedural ventilation time, volume of chest drainage, and total hospital stay and cost. The changes in fraction of inspired oxygen (FiO_2), hepatic enzymes, and estimated glomerular filtration rate after cardiopulmonary bypass during hospitalization were also similar. Two cases of permanent neurological dysfunction occurred in groups A and B. The rate of transient neurological dysfunction in groups A, B, and C was twice that of groups D and E. Hypothermic arrest, whether deep or moderate, was similarly efficacious and safe for patients undergoing surgical repair for AAD. Rates of neurological dysfunction were higher in groups given deep hypothermia.

Keywords: Acute type A aortic dissection, hypothermia, antegrade cerebral perfusion, randomized controlled trial

Introduction

Improvements in strategies for cerebral protection during repair of type A aortic dissection (AAD) in recent decades have not entirely prevented postoperative neurological dysfunction and complications, and these remain important causes of morbidity and mortality [1-4]. The benefits of deep hypothermic circulatory arrest for the protection of vital organs during major cardiovascular surgeries have been demonstrated, particularly for the repair of AAD. Hypothermia with selective antegrade cerebral perfusion (SACP) is considered effective for brain protection during AAD repair [5-10].

With the development of surgical techniques, the operative time required for cardiopulmonary bypass (CPB) during the surgical treatment of AAD has shortened, and there is interest in applying only moderate hypothermic circulatory arrest during the surgery [5, 11]. Many pilot observational studies have reported that moderate, rather than deep, hypothermic circulatory arrest may be equally or more effective for patients undergoing AAD repair [12-16]. However, other studies suggest that deep hypothermic circulatory arrest is more beneficial [17].

The optimal hypothermia condition for SACP has not been determined. Randomized controlled trials (RCTs) are lacking that compare moderate with deep hypothermic circulatory arrest for antegrade selective cerebral perfusion during surgical repair of AAD. The present

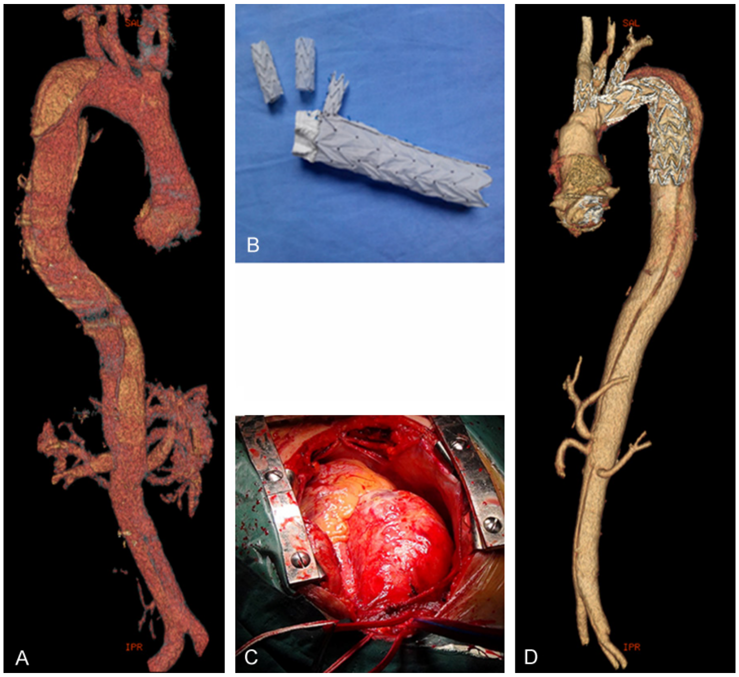

Figure 1. Representative patients with AAD before and after surgical repair of the total aortic arch with covered stents. A. Reconstructive CTA images of the aorta before the surgical repair. B. Covered stents for the main branches of the aorta and the aortic arch. C. Surgical procedure with CPB and antegrade cerebral perfusion. D. Reconstructive CTA images of the aorta after the surgical repair.

RCT evaluated the relative clinical efficacy and safety of 5 hypothermia levels with SACP for patients with ADD during surgery, with particular focus on neurological dysfunction and injuries to vital organs.

Materials and methods

Patients and study protocols

This study was a pilot single-center RCT, which compared the efficacy and safety of different hypothermic conditions for antegrade cerebral perfusion during total arch repair of AAD. The Ethics Committee of Provincial Hospital Affiliated to Anhui Medical University approved the study protocol before its performance, and all the included patients provided signed written consent before enrollment.

Patient inclusion and exclusion criteria

The patients in this study were admitted to our center from 1 January 2009 to 30 April 2016, and all had AAD confirmed by computer tomographic angiography (CTA). All the patients underwent emergency surgical aortic arch repair for acute AAD. Patients with any of the following conditions were excluded from the current study: unstable hemodynamics or confirmed acute myocardial infarction; vital organ ischemia (e.g., intestinal or renal ischemia); severe stenosis of either carotid artery; or transient or persistent cerebral ischemia. In addition, grounds for exclusion were: neurological dysfunction, limb paralysis, or cognitive dysfunction before surgery. Judgments concerning neurological comorbidities before surgery were made by an experienced neurologist who was blinded to the grouping of the patients.

Interventions and patient groups

The 65 patients were randomly and equally apportioned to 5 groups by computer-generated random sequence. This study was single-blinded, and the patients were not aware of the group they were assigned to. The 5 groups differed by hypothermic condition (nasopharyngeal temperature), and blood flow during circulatory arrest and SACP, as follows: Group A (16-18°C, 5 mL/kg); Group B (18-20°C, 10 mL/kg); Group C (20-22°C, 15 mL/kg); Group D (22-24°C, 20 mL/kg); and Group E (24-26°C, 25 mL/kg). Groups A, B, and C were treated with deep hypothermia; groups D and E were treated with moderate hypothermia.

Surgical procedures and perioperative treatment

The included patients were initially assessed, at their admission, by aortic CTA and echocardiography. Intravenous sodium nitroprusside or beta-blockers (such as esmolol) were administered if necessary to maintain a systolic blood pressure of 90-110 mmHg. Intramuscular injection of morphine was used to relieve chest pain and induce sedation.

Before the repair of the AAD, the brachiocephalic artery was cannulated for cardiopulmonary bypass and subsequent unilateral ante-

Table 1. Baseline characteristics of patients included in each group according to hypothermic conditions*

	Group A	Group B	Group C	Group D	Group E
Nasopharyngeal temperature, °C	16-18	18-20	20-22	22-24	24-26
Blood flow for cerebral perfusion, mL/kg	5	10	15	20	25
Age, y	51.5 ± 4.5	51.4 ± 4.4	51.5 ± 4.3	50.5 ± 3.6	51.6 ± 4.5
Male, n (%)	9 (69.2)	9 (69.2)	9 (69.2)	9 (69.2)	9 (69.2)
Body weight, kg	78.3 ± 11.1	77.4 ± 10.4	79.9 ± 9.8	78.4 ± 8.4	79.9 ± 8.9
Hypertension, n (%)	13 (100)	13 (100)	13 (100)	13 (100)	13 (100)
Diabetes mellitus, n (%)	4 (30.8)	4 (30.8)	4 (30.8)	4 (30.8)	4 (30.8)
Chronic obstructive pulmonary disease, n (%)	2 (15.4)	2 (15.4)	2 (15.4)	2 (15.4)	2 (15.4)

*Each group comprised 13 patients.

grade cerebral perfusion. All the patients received cardiac surgeries with the use of standardized cardiopulmonary bypass, which was performed with a Maquet HL 20 roller pump and a membrane oxygenator (Maquet) primed with a solution. During cardiopulmonary bypass, pump flow was set to maintain the mean arterial pressure between 50 and 80 mmHg. The temperature of the blood flow was allowed to drift to < 30°C with active rewarming to > 36°C at the end of the cardiopulmonary bypass.

According to the patient's assigned group, when the goal nasopharyngeal temperature was reached, the unilateral antegrade cerebral perfusion was started based on the predetermined blood flow of the group. The mean perfusion pressure was maintained at 40-60 mmHg. The temperature of the circulatory arrest was identical to the temperature of the fluid for the cerebral perfusion.

The surgical repair of the total arch in AAD involves a system of covered stents with artificial arterial branches (Beijing Yuhengjia Technological, China; **Figure 1**). Briefly, during surgery, the aorta and the main branches of the aorta were exposed, the internal diameters were measured, and suitable covered stents were chosen according to the diameters of the main branches. After the stents were placed into the branches of the aorta, end-to-side anastomoses were performed with the main stents that were placed in the arch of the aorta. To shorten the time of ischemia, distal reperfusion was initiated once the distal anastomosis was completed. The left carotid artery was reconstructed first, after which the brain was perfused bilaterally and the rewarming process was started. After the surgery, the patients were transferred to the intensive care unit (ICU).

Outcomes

The primary outcome of the study was concerned safety, as reflected by the changes in fraction of inspired oxygen (FiO_2), serum alanine aminotransferase (ALT), aspartic transferase (AST), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) within the CPB and perioperative periods.

The secondary outcomes were rates of postoperative transient neurological disorders (TNDs), and permanent neurological disorders (PNDs). TNDs included disorders of consciousness (transient delirium or distress) and manifestations of Parkinson's disease-like symptoms, but without the abnormalities of neurological examinations. PNDs were due to spinal cord ischemia with paralysis of the limbs, as confirmed by neurological examinations such as magnetic resonance imaging and computed tomography scans. The neurological outcomes of the patients in each group were judged by an experienced neurologist who was blinded to the groups of the patients.

Other clinical outcomes such as perioperative mortality, renal dysfunction, and the cost and duration of hospital stay were also observed.

Statistical analyses

Continuous data are presented as mean ± standard deviation. Categorical data are shown as number and frequency. Each set of data was subjected to a normality test for distribution.

Table 2. Perioperative characteristics and clinical outcomes of patients included in each group[a]

	Group A	Group B	Group C	Group D	Group E	P^b
CPB duration, min	178.1 ± 3.5	168.2 ± 6.7	158.7 ± 7.7	138.5 ± 6.6	124.5 ± 5.6	< 0.001
Aortic clamp duration, min	130.2 ± 5.5	119.1 ± 5.4	108.7 ± 8.2	89.2 ± 3.5	77.4 ± 3.4	< 0.001
Hypothermia circulatory arrest duration, min	39.7 ± 3.8	32.8 ± 6.1	28.1 ± 5.2	26.2 ± 5.3	22.1 ± 3.4	< 0.001
SACP duration, min	49.4 ± 10.2	33.6 ± 8.5	28.6 ± 6.6	25.9 ± 5.2	23.2 ± 4.4	< 0.001
Cooling time, min	61.5 ± 7.1	53.6 ± 9.2	44.3 ± 5.5	38.8 ± 4.2	33.5 ± 3.5	< 0.001
Rewarming time, min	121.4 ± 7.3	111.4 ± 8.9	99.5 ± 10.4	86.9 ± 9.2	71.8 ± 9.1	< 0.001
Nasopharyngeal temperature, °C[b]	17.2 ± 1.7	18.7 ± 1.4	21.4 ± 1.2	23.6 ± 1.1	25.2 ± 1.2	< 0.001
Rectal temperature, °C[b]	20.4 ± 1.1	22.3 ± 1.5	24.3 ± 1.2	26.1 ± 1.7	27.1 ± 1.6	< 0.001
Post-procedural ventilation time, min	38.7 ± 22.2	38.5 ± 21.2	37.5 ± 22.2	37.8 ± 22.3	38.1 ± 23.1	0.998
Chest drainage within 24 hour after surgery, mL	623.1 ± 351.2	624.4 ± 353.2	625.1 ± 352.2	626.1 ± 354.2	624.5 ± 352.2	0.999
Blood transfusion volume, mL	3860 ± 270.00	3250 ± 250.00	2870 ± 210.00	2350 ± 200.00	1850 ± 280.00	< 0.001
ICU stay, d	4.85 ± 2.5	4.97 ± 2.5	4.88 ± 2.2	4.78 ± 2.3	4.89 ± 2.7	0.996
Hospital stay, d	24.8 ± 5.3	25.8 ± 5.5	25.1 ± 6.8	23.8 ± 5.6	25.2 ± 6.2	0.966
Cost, 10000 RMB	21.7 ± 1.1	21.9 ± 2.2	21.4 ± 1.2	21.5 ± 2.1	21.1 ± 1.3	0.996

[a]Subjects in each group, n = 13; [b]For beginning cerebral perfusion.

Table 3. Incidence of neurological and renal dysfunction of patients included in each group according to the hypothermia conditions after surgery, n (%)*

	Group A	Group B	Group C	Group D	Group E
TND	2 (15.4)	2 (15.4)	2 (15.4)	1 (7.7)	1 (7.7)
PND	1 (7.7)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Transient renal dysfunction	1 (7.7)	2 (15.4)	1 (7.7)	1 (7.7)	1 (7.7)

*Each group comprised 13 patients.

Differences in continuous and categorical data among the 5 groups were analyzed using analysis of variance (ANOVA). Differences in the data at multiple timepoints among the 5 groups were analyzed using repeated-measures ANOVA. Differences in continuous variables within the same group at different timepoints were analyzed with the paired *t*-test. Statistical analyses were performed with SPSS 16.0 software (SPSS, Chicago, IL, USA). A *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the included patients

Overall, this study included 65 patients with AAD who underwent emergency surgical aortic arch repair (**Table 1**). Briefly, the mean age of the included patients was 51.5 years (range, 25-76 years), and 45 (69.2%) were men. All of the included patients were hypertensive, with blood pressure higher than 165/110 mmHg at admission. Each group (A, B, C, D, and E) consisted of 13 AAD patients. The gender ratio, mean body weight, and rates of diabetes mellitus and chronic obstructive pulmonary disease were statistically similar or identical ($P > 0.05$) among the groups.

Perioperative characteristics of included patients in each group

Patients of the different groups differed significantly with regard to the following (**Table 2**): duration of CPB, aortic clamp, hypothermia circulatory arrest, SACP, cooling, rewarming, and total blood transfusion volume; and nasopharyngeal and rectal temperatures at the beginning of cerebral perfusion. Specifically, patients allocated to the groups with lower perfusion temperature and higher perfusion volume were associated with longer times for aortic clamp, hypothermia circulatory arrest, SACP, cooling and rewarming; and larger total blood transfusion volume. The 5 groups were not significantly different with regard to the following perioperative outcomes: post-procedural ventilation time; volume of chest drainage within 24 hour after surgery; total stay in the ICU or hospital; and the total cost for treatment and hospitalization (*P* all > 0.05).

Postoperative complications and neurological outcomes

All of the patients survived the CPB and surgery. None of the patients experienced severe cardiac dysfunction or multiple organ failure. Eight patients suffered TND (2 each in groups A, B, and C; and 1 each in groups D and E) and

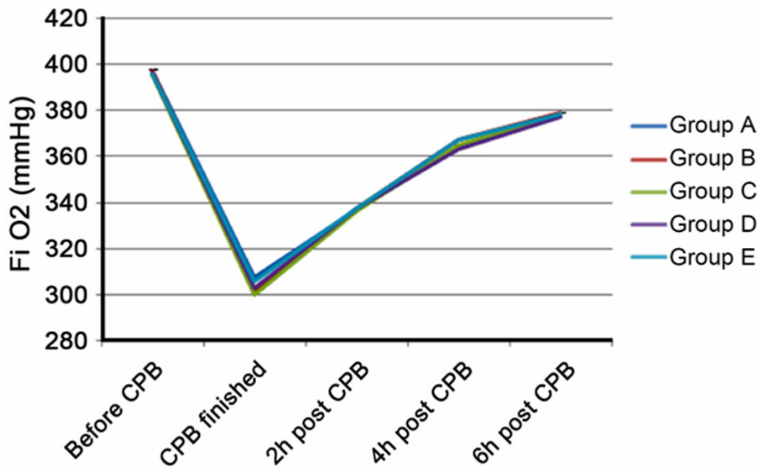

Figure 2. Changes in FiO_2 before CPB and 6 hours within the end of CPB for patients given different hypothermic circulatory arrest conditions during SACP. The changes of FiO_2 were not significantly different among the groups. Compared with before CPB, the FiO_2 was significantly lower at the end of CPB, gradually increasing within the first 6 hours after CPB.

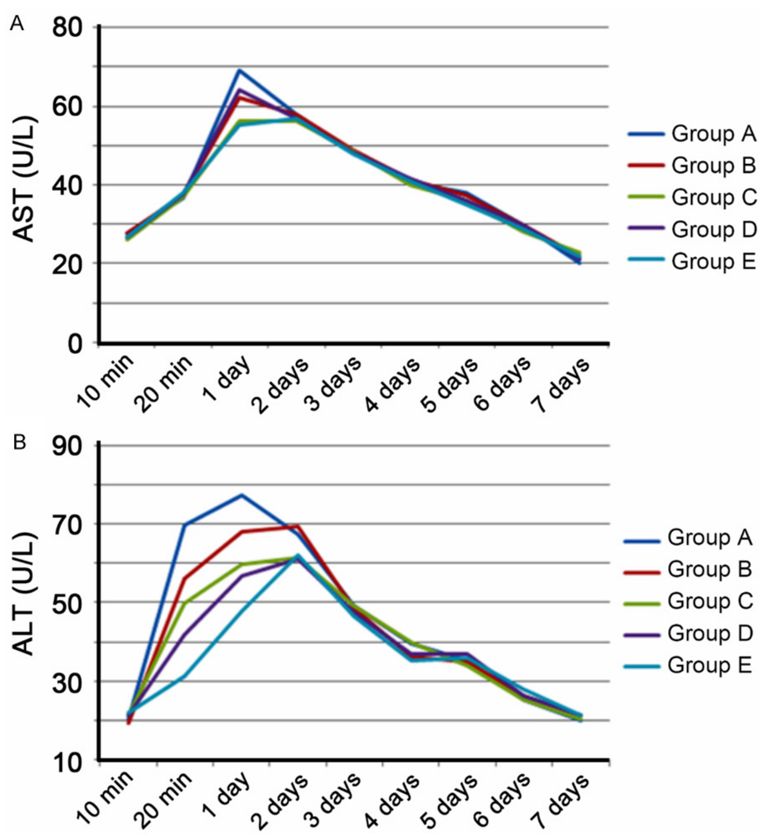

Figure 3. Changes in serum hepatic enzymes within 7 days post-CPB of patient groups given different hypothermic circulatory arrest conditions during SACP. A. Serum AST. B. ALT. The abscissa indicates the time after the initiation of CPB. The changes in AST or ALT were not significantly different among the patient groups. Compared with baseline levels, both AST and ALT were much higher one day after CPB, and gradually decreased within the 7 days after CPB.

2 patients had PND (1 each in groups A and B; **Table 3**). Six patients suffered from transient renal dysfunction during the hospitalization after the CPB and surgery (1 each in groups A, C, D, and E; and 2 in group B).

FiO_2 after CPB

Changes in FiO_2, a marker of cardiopulmonary function, were not significantly different among the patient groups (**Figure 2**); the trends in changes in FiO_2 after CPB were generally coincident among the groups. Briefly, during the CPB, the FiO_2 dropped gradually and reached a minimum at the end of the CPB. FiO_2 then increased gradually within the 6-hour observational period after CPB.

Serum AST and ALT after CPB

Serum AST and ALT levels can be markers of hepatic injury. Changes in serum AST and ALT within the first 7 days after CPB were not significantly different among the 5 groups (**Figure 3**), and the trends in changes in serum AST and ALT after CPB were similar. Briefly, the serum AST and ALT levels increased after the initiation of CPB and reached maximum levels 1-2 days after CPB. These gradually decreased from 2 to 7 days after CPB, and reached levels similar to baseline after 7 days.

BUN and eGFR after CPB

Serum BUN and eGFR are markers of renal function. At each timepoint, serum BUN and eGFR were not significantly different among the 5 groups (**Figure 4**); the trends in the changes in serum BUN and

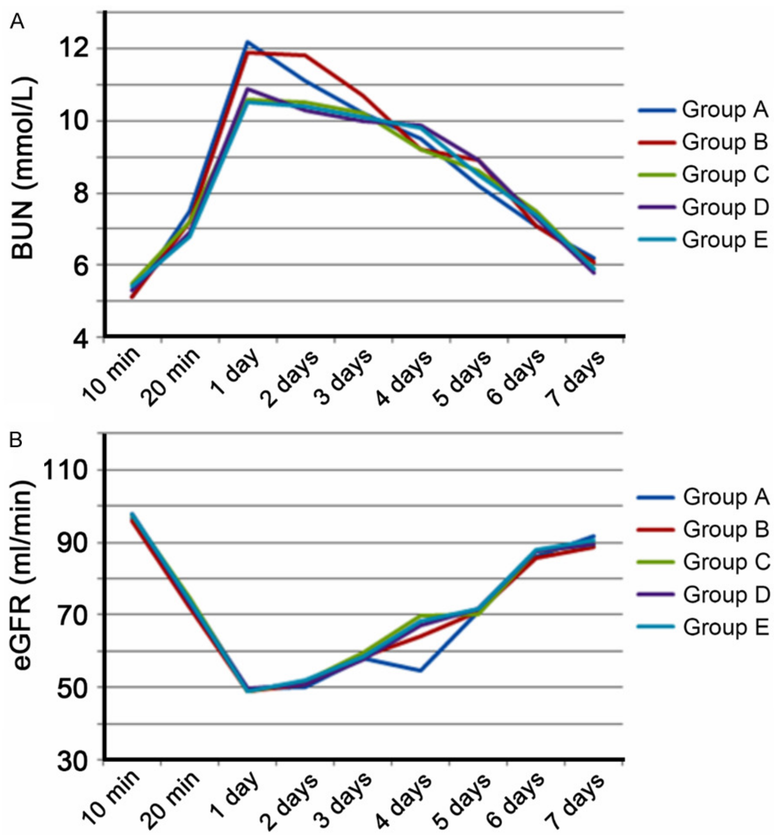

Figure 4. Changes in (A) serum BUN and (B) serum eGFR within the 7 days post-CPB of patient groups given different hypothermic circulatory arrest conditions during SACP. The abscissa indicates the time after the initiation of CPB. BUN or eGFR levels were not significantly different among the patient groups. Compared with baseline levels, (A) serum BUN was significantly higher at 1 day after CPB and decreased gradually within the first 7 days after CPB; (B) eGFR was significantly lower at 1 day after CPB and increased gradually within the 7 days after CPB.

eGFR during the first 7 days after CPB were similar. Briefly, the serum BUN increased after the initiation of CPB and reached maximum levels 1-2 days after CPB; these levels then gradually decreased from 2 to 7 days after CPB. Levels were similar to baseline at 7 days after CPB.

Serum eGFR decreased gradually after the initiation of CPB and reached minimum levels 1-2 days after CPB; these levels then gradually increased from 2 to 7 days after CPB. Levels were similar to baseline, 7 days after CPB.

Discussion

This RCT evaluated the relative clinical efficacy and safety of SACP with hypothermia of various depths, for patients undergoing surgery for AAD repair. To the best of our knowledge, our study is the first RCT to compare the clinical efficacy and safety of different hypothermic conditions in this setting. The patients were randomly assigned to 5 groups according to the hypothermic temperature and blood volume for cerebral perfusion. Patients in groups A (16-18°C, 5 mL/kg), B (18-20°C, 10 mL/kg), and C (20-22°C, 15 mL/kg) were treated with deep hypothermia; those in groups D (22-24°C, 20 mL/kg) and E (24-26°C, 25 mL/kg) underwent moderate hypothermia. All patient groups were comparable regarding post-procedural ventilation time, volume of chest drainage, and total hospital stay and cost. Also similar among the 5 groups were changes in FiO_2, AST, ALT, BUN, and eGFR after CPB during the hospitalization. This suggests that the differences in hypothermic conditions did not differentially affect cardiopulmonary, hepatic, or renal functions. Regarding post-operative neurological dysfunctions, PND occurred in one patient of each of the groups given deeper hypothermic conditions (groups A and B). TND occurred in 2 patients of each of the groups A, B, and C, but only one patient each in groups D and E. These results indicate that the hypothermic circulatory arrest conditions tested were comparable in clinical efficacy and safety for AAD patients undergoing surgical repair of the total arch with artificial stents. However, deep hypothermic conditions (i.e., with nasopharyngeal temperature < 22°C) may be associated with greater risk of postoperative neurological dysfunction. The results suggest that the clinical effects of moderate hypothermic arrest may equal that of deeper hypothermia under these conditions.

The results of our study are consistent with a few previously published reports that moderate hypothermic circulatory arrest was at least as effective as deep hypothermic circulatory arrest for SACP in patients with AAD. In a retrospective study from Emory University, 288 patients with AAD who underwent emergency surgical repair were grouped as moderate (> 24°C) or deep hypothermic circulatory arrest (≤ 24°C) [16]. There were no significant differences in duration of CPB, cross-clamp, or hypothermic circulatory arrest between the 2 groups; nor were there differences in rates of complications such as stroke, TND, or dialysis-dependent renal failure.

A recently published prospective study from China also confirmed the feasibility of moderate hypothermic circulatory arrest for surgical repair of emergency AAD [12]. In that study, 74 consecutive patients with acute AAD who underwent emergency total arch replacement and frozen elephant trunk implantation received deep (< 20°C) or moderate (20-28°C) hypothermic circulatory arrest. The 2 groups were equivalent in operative mortality and morbidity and hepatic and renal functions.

Interestingly, a few studies have even suggested potential clinical benefits of moderate over deep hypothermic circulatory arrest in these patients. In an observational study of 211 consecutive patients who underwent surgical repair for AAD, moderate hypothermic circulatory arrest (< 20°C) was independently associated with a lower risk of composite mortality and major adverse cardiac and cerebrovascular events [14]. Another study compared moderate and deep hypothermia circulatory arrest during total aortic arch replacement, and found that the former was associated with a significantly lower risk of neurologic dysfunctions (transient and permanent; odds ratio = 0.385) [15]. The authors concluded that moderate hypothermic circulatory arrest was safe and effective for protecting cerebral and visceral organs, with a shorter circulatory arrest time.

Altogether, the results of these studies suggest that moderate hypothermic circulatory arrest may be more effective than deep for preventing neurological dysfunction. Our present results also seem to support this conclusion, since deep hypothermic conditions (e.g., with nasopharyngeal temperature < 22°C) appeared to be associated with more cases of neurological dysfunction. Moderate hypothermic circulatory arrest may have neurological benefits because the lower temperature and prolonged circulatory arrest of deep hypothermic circulatory arrest lead to conditions that deteriorate neurologic systems. Such conditions include activation of an inflammatory response [18, 19], coagulation dysfunction [20, 21], and oxidative stress related to ischemia-reperfusion injury [22, 23]. The exact mechanisms deserve further investigation.

Our study has limitations which should be considered when interpreting the results. First, although an RCT, this study comprised a small number of patients and may be statistically underpowered for clinical outcomes, such as the proportions of patients with neurological dysfunction. Secondly, the neurologic outcomes were defined as either transient or permanent dysfunction, and this could be considered subjective and biased judgements of the neurologist. Moreover, the differences regarding the proportions of patients receiving ACP, as well as the differences of the procedural characteristics, such as the time of CPB and AAC, may have potentially affected the neurological outcomes among the groups. In addition, the definitions of moderate and deep hypothermic circulatory arrest were based on our experience in clinic, and should be standardized for easy comparisons. Finally, the size of the applied stents was measured during the operation, and a preoperative CTA examination may be helpful for the accurate selection of stents.

In conclusion, the results of our study indicate that moderate or deep hypothermic arrest had similar clinical efficacy and safety for AAD patients undergoing surgical repair, although deep hypothermic conditions may have been associated with more cases of neurological dysfunction. Our study highlights the potential feasibility and neurological benefits of moderate hypothermic circulatory arrest for SACP in this setting.

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Disclosure of conflict of interest

None.

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