

Moderate hypothermic circulatory arrest in total arch repair for acute type A aortic dissection: clinical safety and efficacy

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Background: Continued debates exist regarding the optimal temperature during hypothermic circulatory arrest (HCA) in aortic arch repair for patients with type A aortic dissection (TAAD). This study seeks to examine whether the use of moderate HCA in emergency aortic arch surgery provides comparable operative outcomes to deep HCA for patients with acute TAAD.

Methods: We prospectively enrolled 74 consecutive patients (mean age 47.7 ± 9.8 years, 54 males) with acute TAAD, who underwent emergency total arch replacement and frozen elephant trunk implantation under HCA ($18\text{--}28^\circ\text{C}$) with unilateral selective antegrade cerebral perfusion (uSACP). Patients were divided into two groups based on the nasopharyngeal temperature at the initiation of HCA: deep HCA (DHCA, $<20^\circ\text{C}$) in 35 (47.3%) and moderate HCA (MHCA, $20\text{--}28^\circ\text{C}$) in 39 (52.7%). Operative outcomes including mortality, morbidity and visceral organ functions were compared between the two groups.

Results: The mean times of cardiopulmonary bypass (CPB) and aortic cross-clamp were 211 ± 54 and 238 ± 62 minutes ($P=0.053$) and 118 ± 27 and 142 ± 45 minutes ($P=0.005$) in the MHCA and DHCA groups, respectively. Operative mortality did not differ between two groups (10.2% in MHCA *vs.* 14.3% in DHCA groups, $P=0.862$). Nor did the incidence of morbidities differ between the two groups ($P>0.05$). The temporal trend in the changes of postoperative levels of creatinine, aspartate aminotransferase, total bilirubin and lactate did not differ between two groups ($P>0.05$). Multivariate analysis found that the temperature during HCA (MHCA *vs.* DHCA) did not affect operative mortality, morbidities and neurologic complications. Instead, CPB time (in minutes) was the risk factor for operative mortality (odds ratio, 1.032; 95% confidence interval, 1.004–1.061; $P=0.023$).

Conclusions: Moderate HCA is associated with equivalent operative mortality and morbidity and visceral organ functions compared to deep HCA in patients with acute TAAD undergoing total arch replacement under uSACP. This study implies the clinical safety and efficacy of moderate HCA in emergency aortic arch repair for such patients, which provides equivalent cerebral and visceral organ protection while decreasing CPB and cross-clamp times without increasing the risk of operative mortality and morbidity.

Keywords: Aortic dissection; hypothermia; heart arrest; outcome; mortality

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Introduction

During the past decades, deep hypothermic circulatory arrest (HCA) has been widely used and is considered by many to be an effective modality in surgical repair of acute type A aortic dissection (TAAD) (1-4). Although the use of HCA in adjunction with selective antegrade cerebral perfusion (SACP) has improved the surgical results (5-8), these complex procedures are still associated with significantly high operative mortality and morbidity and there has been no consensus on the optimal temperature during HCA.

Due to the adverse effects of deep HCA (DHCA), a recent development in TAAD repair has been a departure from the use of deep hypothermia and excellent results have been achieved with the use of warmer temperatures in aortic arch repair (5-11). This has raised the question of whether DHCA affords any additional benefits to justify its adverse effects (12).

In the past decade, the strategy of temperature management in our center has evolved from the use of deep HCA to moderate HCA (MHCA) for repair of acute TAAD. In this study we seek to examine whether MHCA provides equivalent early outcomes as DHCA in patients with acute TAAD undergoing total arch replacement and frozen elephant trunk implantation under unilateral SACP (uSACP).

Methods

Patients

The present study is part of a prospective clinical trial. The Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University approved the study protocol (File # 2014019). Written consent was obtained from the patients and their relatives before the operation.

Between August 2014 and July 2015, we enrolled 74 patients who underwent emergency aortic arch repair for acute TAAD. The median time from symptom onset to surgery was 39 hours (mean 59.0 ± 59.5 , range 1–270). Mean age was 47.7 ± 9.8 years and 54 were male (73.0%). Mean body mass index was 26.2 ± 3.6 kg/m². Chest pain was present in 69 patients (93.2%). Based on the nasopharyngeal temperature at the initiation of HCA, patients were divided into groups with lower and higher temperatures, defined as the DHCA and MHCA groups (13): (I) the DHCA group: <20 °C ($n=35$, 47.3%); (II) the MHCA group: 20 – 28 °C ($n=39$, 52.7%).

As shown in Table 1, the two groups were similar in age, body mass index and other preoperative variables ($P>0.05$), except the MHCA group had a higher percentage

of hypertension (89.7% *vs.* 71.4%, $P=0.045$) and cardiac tamponade (30.8% *vs.* 11.4%, $P=0.044$). Preoperative visceral functions as indicated by the concentrations of creatinine (kidney), aspartate aminotransferase and total bilirubin (liver) and lactate (bowels) (14) did not differ significantly between the two groups ($P>0.05$; Table 1).

Exclusion criteria included patients with subacute and chronic TAAD, intramural hematoma, penetrating aortic ulcer and traumatic aortic transection and death prior to surgical repair.

Surgical techniques

Our surgical technique has been previously described in detail (15-17). Specifically, right axillary artery cannulation is used for cardiopulmonary bypass (CPB) and unilateral SACP. Upon reaching the goal nasopharyngeal temperature of 18 – 28 °C, uSACP is initiated at a flow rate of 5 – 10 mL/kg/min and a mean perfusion pressure of 40 – 60 mmHg is maintained during CPB. The temperature for circulatory arrest and the temperature for SACP were equal. The procedure involves deployment of an open stent graft, Cronus® (MicroPort, Shanghai, China) into the descending aorta and total arch replacement with a 4-branched vascular graft (Maquet Cardiovascular, Wayne, NJ). The open stent graft was 10 cm in length and 24–28 mm in diameter. The distal landing zone is above T6 in most cases (16). Deployment simply involves gripping the handle in one hand and pulling out the pull wire with the other hand; the stent graft expands automatically, usually within seconds (15). To minimize the time of ischemia, distal reperfusion is initiated once the distal anastomosis is completed; the left carotid artery is reconstructed first, after which the brain is perfused bilaterally and rewarming is started.

Definition of endpoints

In this study, operative mortality refers to all deaths, regardless of cause, occurring during the same hospitalization in which the operation was performed, even if after 30 days and after discharge from the hospital but within 30 postoperative days (18). Operative morbidities include reexploration for bleeding, low cardiac output syndrome, renal failure requiring dialysis, stroke and paralysis.

Statistical analysis

All statistical analyses were performed with SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Data are expressed as mean

Table 1 Preoperative patient profile

Variable	MHCA group (n=39, %)	DHCA group (n=35, %)	P value
Age (year)	48.6±10.7	46.7±8.7	0.402
Male	30 (76.9)	24 (68.6)	0.419
Body mass index (kg/m ²)	26.1±4.0	26.5±3.0	0.640
Obesity (BMI >30 kg/m ²)	6 (15.4)	4 (11.4)	0.876
Comorbidities			
Hypertension	35 (89.7)	25 (71.4)	0.045
Diabetes mellitus	2 (5.1)	2 (5.7)	1.000
Bicuspid aortic valve	0 (0)	3 (8.6)	0.202
Prior cerebrovascular disease	2 (5.1)	1 (2.9)	1.000
Coronary artery disease	4 (10.2)	0 (0)	0.152
History of smoking	18 (46.2)	17 (48.6)	0.835
Marfan syndrome	1 (2.6)	3 (8.6)	0.339
Hours from onset to surgery	60±58 [1–240]	56±64 [5–270]	0.782
Cardiac tamponade	12 (30.8)	4 (11.4)	0.044
Laboratory tests			
Creatinine (μmol/L)	83.9±24.4	89.9±31.2	0.360
Aspartate aminotransferase (IU/L)	31.1±33.6	32.1±20.7	0.139
Total bilirubin (μmol/L)	23.8±13.0	24.8±15.3	0.765
Lactate (mmol/L)	1.7±1.1	1.5±0.7	0.258
Troponin I (ng/mL)	0.7±3.6	0.3±0.7	0.307
CT angiogram and echocardiogram			
Aortic root size (mm)	41.3±5.9	40.9±8.6	0.831
Ascending aortic size (mm)	45.3±5.5	44.7±7.5	0.713
Severe aortic regurgitation	5 (12.8)	9 (25.7)	0.157
Left ventricular ejection fraction	0.62±0.05	0.64±0.06	0.129

DHCA, deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest.

± standard deviation (SD) or number and percentages as appropriate. Student's *t*-test or Wilcoxon rank sum test and *chi*-square or Fisher's exact tests were used for comparisons as appropriate. Risk factors for operative mortality and morbidities were identified with multivariate analysis using a forward stepwise binary logistic regression model. The differences in the variations over time of postoperative serum levels of aspartate aminotransferase, total bilirubin, creatinine and lactate were evaluated using a mixed effect analysis of variance model. All statistical tests were 2-sided and any *P* value of <0.05 was considered statistically significant.

Results

Operative data

At the start of circulatory arrest, the mean nasopharyngeal

temperature was 21.7±2.5 °C for the entire series. In the DHCA group, HCA started at a significantly lower temperature than in the MHCA group (19.2±0.7 *vs.* 24.0±1.0 °C; *P*<0.01). The time of CPB was shorter in the MHCA group than in the DHCA group, which almost reached statistical significance (211±54 *vs.* 238±62 minutes, *P*=0.053). The time of aortic cross-clamp was significantly shorter in the MHCA group than the DHCA group (118±27 *vs.* 142±45 minutes, *P*=0.005). The two groups had similar times of HCA (28±8 *vs.* 29±9 minutes, *P*=0.465) and operation (8.5±1.9 *vs.* 9.2±2.0 hours, *P*=0.108), respectively (Table 2). Of note, the HCA time was 30 minutes or less in 68.9% of patients (51/74) and >50 minutes in only 1 patient (1.3%) of the entire cohort.

Composite graft root replacement was required in 41.0% (16/39) *vs.* 40.0% (14/35) of patients in the MHCA

Table 2 Operative data

Variable	MHCA group (n=39, %)	DHCA group (n=35, %)	P value
Nasopharyngeal temperature (°C)	24.0±1.0	19.2±0.7	<0.01
Durations			
Cardiopulmonary bypass time (min)	211±54	238±62	0.053
Aortic cross-clamp time (min)	118±27	142±45	0.005
Hypothermic circulatory arrest time (min)	28±8	29±9	0.465
Operation time (hour)	8.5±1.9	9.2±2.0	0.108
Additional procedures			
Composite graft root replacement	16 (41.0)	14 (40.0)	0.929
Coronary artery bypass grafting	3 (7.7)	0	0.278

DHCA, deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest.

vs. DHCA groups, respectively ($P=0.929$). Concomitant coronary artery bypass grafting was performed in three patients of the MHCA group (7.7%).

Operative mortality and morbidity

Operative mortality was 12.2% (9/74), including 4 deaths in the MHCA (10.2%) and 5 in the DHCA groups (14.3%), respectively. However, mortality rate did not differ significantly between the two groups ($P=0.862$). The leading cause of death was multiorgan failure, identified in 5 (6.7%, 5/74) of the 9 expired patients (55.5%), with 2 in the DHCA group and 3 in the MHCA group, respectively. Other causes included cerebral hemorrhage in 2 patients (5.7%, 2/35) of the DHCA group, cerebral infarct in 1 (2.6%, 1/39) and sepsis in 1 (2.6%, 1/39) of the MHCA group, respectively.

The total amount of postoperative drainage up to 7 postoperative days did not differ between the two groups (2,937 *vs.* 2,850 mL, $P=0.874$). Nor were there any difference in the transfusion of blood products ($P>0.05$) and the incidence of reexploration for bleeding (10.2% in MHCA *vs.* 8.6% in DHCA, $P=1.000$) between the two groups. No statistical difference was found in the incidence of renal failure requiring dialysis (7.7% in MHCA *vs.* 14.3% in DHCA, $P=0.591$). A similar percentage of patients sustained stroke (5.1% *vs.* 8.6%, $P=0.900$) and paralysis (7.7% *vs.* 5.7%, $P=1.000$) in each group, respectively. There were no statistical differences between the MHCA and DHCA group in the incidences of low cardiac output, prolonged ventilation, sepsis and multiorgan failure ($P>0.05$; Table 3).

Postoperative vital organ functions

In the MHCA and DHCA groups, a significant temporal effect with increases in the concentrations of creatinine, aspartate aminotransferase, total bilirubin and lactate was observed postoperatively ($P<0.05$). Creatinine reached its peak concentration ($P=0.015$) at postoperative day 2 in the MHCA group and at day 3 in the DHCA group. In both groups, the peak level was at postoperative day 2 for aspartate aminotransferase ($P=0.028$), and at day 1 for total bilirubin ($P<0.01$) and lactate at ($P<0.01$), respectively. However, mixed effect analysis of variance modeling revealed that these temporal trends did not differ between the MHCA and DHCA groups in the levels of creatinine ($P=0.611$), aspartate aminotransferase ($P=0.144$), total bilirubin ($P=0.605$) and lactate ($P=0.453$) as shown in Figures 1–4.

Risk factors for operative mortality and morbidities

In multivariable analysis, the temperature during HCA (MHCA *vs.* DHCA) did not affect the operative mortality [odds ratio (OR), 0.799; 95% confidence interval (CI), 0.079–8.126; $P=0.849$], morbidities (OR, 1.909; 95% CI, 0.389–9.353; $P=0.425$) and neurologic complications (OR, 0.661; 95% CI, 0.180–2.428; $P=0.532$). The cardiopulmonary time (in minutes) was the only risk factor for operative mortality (OR, 1.032; 95% CI, 1.004–1.061; $P=0.023$). No risk factors were identified for operative morbidities and neurologic events (Table 4).

Discussion

Acute TAAD is a catastrophic event with very high risk

Table 3 Operative outcomes

Variable	MHCA group (n=39, %)	DHCA group (n=35, %)	P value
Operative mortality	4 (10.2)	5 (14.3)	0.862
Morbidities			
Reexploration for bleeding	4 (10.2)	3 (8.6)	1.000
Low cardiac output syndrome	1 (2.6)	0	1.000
Dialysis-dependent renal failure	3 (7.7)	5 (14.3)	0.591
Stroke	2 (5.1)	3 (8.6)	0.900
Paralysis	3 (7.7)	2 (5.7)	1.000
Prolonged ventilation (>48 hours)	3 (7.7)	5 (14.3)	0.591
Sepsis	5 (12.8)	6 (17.1)	0.602
Multiorgan failure	6 (15.4)	4 (11.4)	0.876
Bleeding and blood transfusions			
Total drainage up to 7 postop. days (mL)	2,937±2,205	2,850±2,408	0.874
Postoperative hemoglobin (g/dL)	9.7±2.0	9.4±2.2	0.389
Packed red blood cells (mL)	1,431±1,195	1,877±1,704	0.479
Fresh frozen plasma (mL)	790±619	680±521	0.415
Platelet concentrate (unit)	1.2±1.5	1.6±2.2	0.558
Length of hospital stay (day)	15.2±8.9	16.6±6.7	0.437
Length of intensive care unit stay (day)	5.6±7.4	6.6±6.6	0.292

DHCA, deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest.

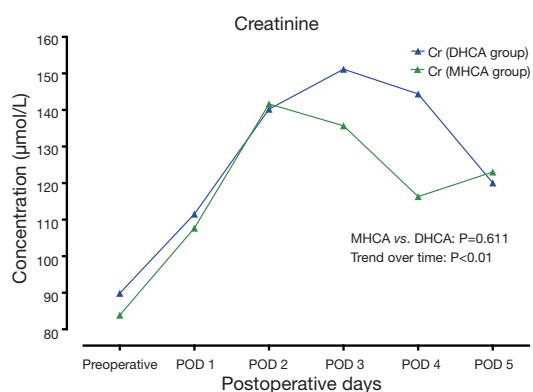


Figure 1 Changes of serum creatinine (Cr) over time in the deep and moderate hypothermic circulatory arrest groups.

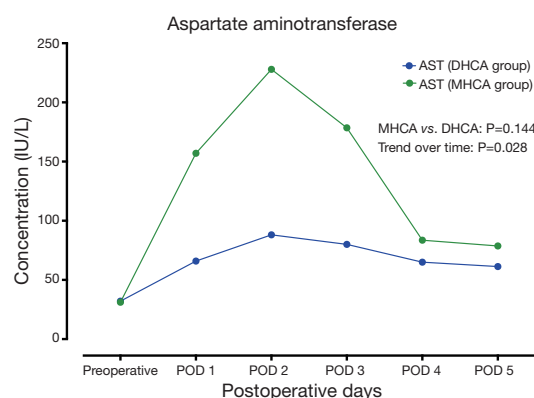


Figure 2 Changes of serum aspartate aminotransferase (AST) over time in the deep and moderate hypothermic circulatory arrest groups.

of mortality and morbidity (19,20). Although DHCA with or without adjunctive cerebral perfusion has been an important tool for cerebral protection in aortic arch surgery and its safety was proven over the past two decades, continued debates exist regarding the use of DHCA (1-3). Some studies have shown the adverse effects of DHCA, such as prolonged CPB time which leads to increased

systemic inflammatory response and subsequent coagulation disorders, postoperative bleeding and higher need for blood transfusion, and organ dysfunction (6,10,11). As a result, the past decade has seen a departure from traditional DHCA techniques to warmer temperatures in HCA. Moreover, several studies (21-24) have compared the techniques of DHCA to MHCA and some have shown that aortic arch

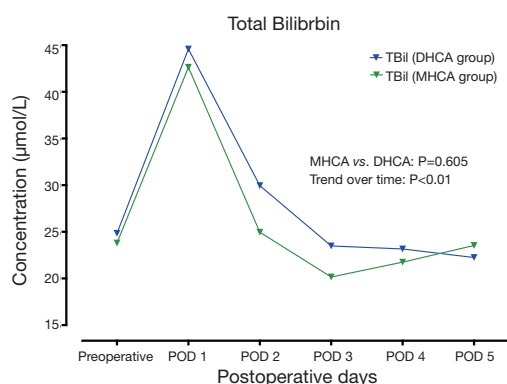


Figure 3 Changes of serum total bilirubin (TBil) over time in the deep and moderate hypothermic circulatory arrest groups.

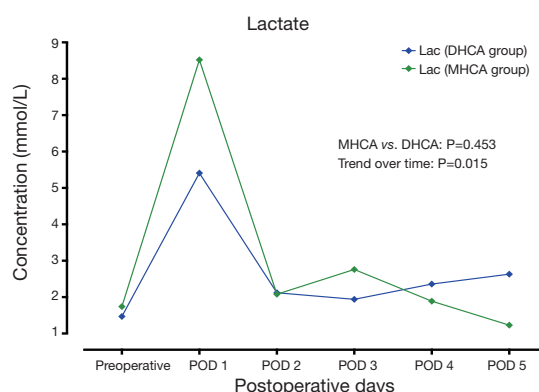


Figure 4 Changes of serum lactate (Lac) over time in the deep and moderate hypothermic circulatory arrest groups.

Table 4 Risk factors for operative mortality morbidities and neurologic deficits

Endpoints/risk factors	Odds ratio	95% confidence interval	P value
Operative mortality*			
Cardiopulmonary bypass time (min)	1.032	1.004–1.061	0.032
Temperature (DHCA vs. MHCA)	0.799	0.079–8.126	0.849
Operative morbidity [#]			
Temperature (DHCA vs. MHCA)	0.661	0.180–2.428	0.532
Neurologic deficits [§]			
Temperature (DHCA vs. MHCA)	1.909	0.389–9.353	0.425
Circulatory arrest time (min)	0.972	0.893–1.059	0.519

DHCA, deep hypothermic circulatory arrest; MHCA, moderate hypothermic circulatory arrest; *, variables considered in the analysis included temperature (DHCA vs. MHCA), cardiopulmonary bypass time and cross-clamp time; [#], variables considered in the analysis included age, hypertension, temperature (DHCA vs. MHCA), cardiopulmonary bypass time, cross-clamp time and HCA time; [§], variables considered in the analysis included temperature (DHCA vs. MHCA), cardiopulmonary bypass time and cross-clamp time.

surgery could be performed safely under MHCA rather than DHCA (6-8,25). However, it is difficult to compare DHCA and MHCA directly because most centers have achieved good outcomes with a single strategy. Although Chen and associates compared the early outcomes of MHCA *vs.* DHCA in a large series of 288 patients with acute TAADs, total arch repair was performed only in 9 (11.0%) *vs.* 23 (11.2%) patients of the DHCA *vs.* MHCA groups, while hemiarch repair was the procedure in 88.9% (256/288) of their patients (26). In contrast, all patients in this study were managed with total arch replacement, which provides an opportunity to compare directly the impact of moderate and deep HCA on operative outcomes while all other confounding factors (patients, cannulation, cerebral perfusion and surgical technique) are similar.

Although some studies (21-24) have suggested that

MHCA may not provide adequate protection for the neurologic system and visceral organs, especially with prolonged duration of circulatory arrest, some high-volume centers have achieved excellent results with the use of warmer temperatures in aortic arch repair (4-10). Experimental animal models (27) also showed that further cooling did not decrease brain oxygen consumption efficiently. Over the past decade, our protocol of HCA has evolved considerably as we accrued more experience, and now we routinely perform arch surgery at 25–28 °C, a temperature that is higher than that used by other institutions (1-3). The results of this study show that the use of MHCA in total arch replacement and frozen elephant trunk under unilateral cerebral perfusion was not associated with increased risks of operative mortality and morbidities, neurological complications and impaired visceral functions (the liver, kidney and bowels), which implies that

that aortic arch surgery can be safely performed under MHCA and uSACP in the emergency settings for patients with acute TAAD.

Neurologic complications after arch surgery are believed to be mainly associated with the use of DHCA (23,24,28). SCAP has increasingly been adopted to minimize the incidence of neurologic complications (29,30). In this study, the incidence of neurologic complications did not differ between the DHCA and MHCA groups, nor was the temperature in HCA identified as a risk factor for neurologic complications. Our results suggest that MHCA could provide equivalent cerebral protection as DHCA in emergency aortic arch surgery for patients with acute TAAD. In this study, the time of HCA was not a risk factor for neurologic complications either, which is inconsistent with other reports in which HCA time was identified as a risk factor for stroke or temporary neurologic dysfunction (14,31). A possible explanation for this difference may be that the HCA time was >30 minutes in only 31.1% (23/74) and >50 minutes in only 1.3% (1/74) of patients in this series. Mounting experimental and clinical evidence (28,29) have suggested that the safety limit of HCA might approximate 30–40 minutes. When the HCA time exceeds 45 minutes, the incidence of neurologic deficit will increase drastically (32). Based on the results of this study we speculate that a HCA time of ≤ 30 minutes may not affect the incidence of neurologic deficits considerably.

Although it is believed that HCA, especially DHCA, can induce coagulopathy (33), results in literature are conflicting. Zierer and colleagues (34) found a marked reduction in the mean chest tube drainage, CPB time and intensive care unit stay in patients undergoing MHCA compared to those with DHCA. However, Harrington and associates (22) reported that DHCA was not associated with increased postoperative hemorrhage. This study found no significant difference in the postoperative drainage and the transfusion requirements between the two groups, which indicates that both MHCA and DHCA may have similar impacts on the blood elements and the coagulation process in this cohort of patients with acute TAAD.

A major concern of using more moderate levels of hypothermia is a compromise in the suppression of visceral organ metabolism as opposed to DHCA (12). Clinically, the kidneys are most sensitive to ischemia among the viscera, followed by the liver and the bowel (5,8). The most frequent indicator of visceral organ injury identified in aortic surgery is acute renal failure. In this study, there was no significant difference in the incidence of dialysis-dependent renal failure and the temporal trend in the changes of creatinine

levels between the two groups, nor was any statistical difference identified in the temporal trend of the hepatic and intestinal functions following emergency total arch repair. Given that both groups had similar visceral ischemia (HCA) times, it does imply that moderate hypothermia in the current study provided equivalent visceral protection compared with deep hypothermia.

Although the CPB time did not differ between the MHCA and DHCA groups, CPB time was identified as the only risk factor that significantly affects operative mortality, which is consistent with the finding of our previous study (17) and that of others (35). DHCA is associated with longer times of CPB, aortic cross-clamp and the procedure because it entails longer periods for cooling and rewarming, and longer time for hemostasis, with a potential increase in the risk of ischemic reperfusion injury (21–23). Taken the average CPB times in both groups, the risk of operative mortality in the DHCA group (238 minutes) would be 2.3-fold higher than in the MHCA group (211 minutes). Given the similar outcomes in terms of operative mortality and morbidity, and neurologic and visceral protections in the MHCA and DHCA groups, an important implication is that MHCA may be a better approach in emergency aortic arch repair for patients with acute TAAD by avoidance of posing such patients to the longer CPB times and potential adverse risks of DHCA (12), including multiorgan endothelial dysfunction (23).

Study limitations

This study has several imitations although it is part of a prospective clinical trial. Most important is its relatively small sample size compared with other large series, which affects the power of statistical analysis, especially in the identification of risk factors. It is also limited by the absence of sensitive and specific indicators of visceral organ injury. The variables chosen in this study measuring visceral organ functions are unspecific and influenced by a lot of other factors. Another concern pertains to the young average age of patients in this study (47 years) although senior age is not a contraindication for aortic arch reconstruction in our center. Therefore, data in this study may not be applicable to older patients who might be more prone to neurologic ischemic events. Furthermore, as no consensus exists on the levels of temperature for HCA (12), both groups in this study would be considered as DHCA by the Johns Hopkins definition and therefore caution should be taken when interpreting the results of this study. In addition, this study represents a single-center experience susceptible to

inherent selection biases. Despite these limitations, the homogeneous nature of this study with respect to patients, cerebral perfusion method and surgical procedure does allow for a more intuitive comparison of the impacts of MHCA *vs.* DHCA.

Conclusions

The results of this study show that the temperature in HCA did not affect operative mortality in aortic arch surgery for patients with acute type A dissection. This study implies the clinical safety and efficacy of moderate HCA in emergency aortic arch repair for such patients, which can provide comparable cerebral and visceral organ protection while decreasing CPB and aortic cross-clamp times without increasing the risk of operative mortality and morbidity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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