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BRAIN AND LOWER BODY PROTECTION DURING AORTIC ARCH SURGERY

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Abstract

Background. Deep hypothermic circulatory arrest (DHCA) at [?]20°C for aortic arch surgery has been widely used for decades, with or without cerebral perfusion (CP), antegrade (ACP) or retrograde. In recent years nadir temperature progressively increased to 26-28 °C (moderately hypothermic circulatory arrest, MHCA), adding ACP. Aim of this multicentric study is to evaluate early results of aortic arch surgery and if DHCA with 10-minute of cold reperfusion at the same nadir temperature of the CA before rewarming (delayed rewarming, DR) can provide a neuroprotection and a lower body protection similar to that provided by MHCA+ACP. **Methods.** Two-hundred-ten patients were included in the study. DHCA+DR was used in 59 patients and MHCA+ACP in 151. Primary endpoints were death, neurologic event (NE), temporary (TNE) or permanent (permanent neurologic deficit, PND), and need of renal replacement therapy (RRT). **Results.** Operative mortality occurred in 14 patients (6.7%), NEs in 17 (8.1%) and PNDs in 10 (4.8%). Twenty-three patients (10.9%) needed RRT. Death+PND occurred in 21 patients (10%) and composite endpoint in 35 (19.2%). Intergroup weighed logistic regression analysis showed similar prevalence of deaths, NDs and death+PND, but need of RRT (OR 7.39, CI 1.37-79.1) and composite endpoint (OR 8.97, CI 1.95-35.3) were significantly lower in DHCA+DR group compared with MHCA+ACP group. **Conclusions.** The results of our study demonstrate that DHCA+DR has the same prevalence of operative mortality, NE and association of death+PND than MHCA+ACP. However, the data suggests that DHCA+DR when compared with MHCA+ACP provides better renal protection and reduced prevalence of composite endpoint.

INTRODUCTION

The advent of deep hypothermic circulatory arrest (DHCA) was a key point for the surgical treatment of the pathologies involving the aortic arch. The level of hypothermia [?]20°C revolutionized and made approachable, with reasonable results, partial or total aortic arch replacement. However, the relatively high incidence of neurologic events (NEs) argued for the use of cerebral protection, retrograde cerebral perfusion

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(RCP) or antegrade cerebral perfusion (ACP), selective (SACP) or unilateral (UCP). Indeed, both methods were successful and the possibility to perform more and more complex surgery increased the confidence of surgeons, improving the clinical outcomes.

More recently, the widespread use of ACP pushed to increase the nadir temperature to 28°C (moderately hypothermic circulatory arrest, MHCA) to reduce some complications related to long cardiopulmonary bypass (CPB). DHCA was perceived as a strategy not only less effective, but potentially harmful, and MHCA+ACP became the standard of care. An experimental study[1], published in 2001, suggested that a 20-minute cold reperfusion after DHCA before rewarming reduces the cerebral damages due to excess of glutamate, but this finding was not followed by clinical application. Another research, published more than 10 years after, found a reduction of NDs after 10-minute of cold perfusion before rewarming[2] after DHCA, but there were no further studies and consequently delayed rewarming (DR) was never included as a strategy of neuroprotection during arch surgery.

Aim of the study is to evaluate early results of aortic arch surgery and if DHCA with 10-minute of cold reperfusion at the same nadir temperature of the CA before rewarming (delayed rewarming, DR) can provide a neuroprotection and a lower body protection similar to that provided by MHCA+ACP.

MATERIAL AND METHODS

Patient population

Each site's institutional review board has approved this study. Because of its retrospective nature, the local ethics committees waived the need for specific patient consent.

This is a retrospective cohort observational multicentric study that utilizes data from 7 institutional databases of patients who underwent elective aortic arch surgery under circulatory arrest (CA), from 2018 till 2021.

Patients with acute aortic syndrome or with chronic aortic dissections were excluded. Two-hundred-fifty patients were included and stratified according to the adjunctive CP techniques used, if any. Forty cases were excluded because of missing data (n=11) or techniques not included in the analysis (n=26). Three more cases, defined as "outliers", were excluded as well. Finally, the cases included in the analysis were 210. Patients were then divided in two groups according to the surgical strategy. The first group (n=59) included patients operated on during DHCA at [?] 20degC, without any CP, and DR (DHCA+DR group). Cerebral and lower body CA coincided. The second group (n=151) included patients operated on during MHCA, median temperature 26degC, and ACP (MHCA+ACP group). The brain was continuously perfused and the duration of CA involved only the lower body.

Goal of the study

Primary endpoints were operative mortality, NE and need of renal replacement therapy (RRT). Secondary endpoints were time to extubation, need of tracheostomy and intensive care unit (ICU) length of stay (LOS). Operative mortality included 30 day or in-hospital mortality. NEs included stroke (defined as a cerebrovascular accident confirmed by radiologic imaging, computed tomography or magnetic resonance imaging) and seizures, localized or generalized, with or without positive radiologic imaging. According the clinical outcome, NEs were classified as temporary (TNEs) or permanent neurologic deficits (PNDs). The effect of temperature on lower body protection was evaluated by acute kidney injury (AKI) necessitating RRT. Changes in kidney function were also analysed according the KIDGO criteria[3]. Primary endpoints were analysed separately, grouped as death and PND or as composite endpoint (death, PND and need of RRT).

Results were reported for the whole statistics and were compared as well between the two groups.

Statistical analysis

Descriptive statistical methods were applied to depict the study population at baseline. Continuous, variables are presented as the median and interquartile range (25^{th} and 75^{th} percentiles). Categorical variables

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are presented as counts and percentages Differences between groups were compared with Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables are summarized as the number and percentage of subjects in each category, and differences were compared with the Pearson chi-square test.

Missing data were not superior to 10%. Pattern of missing values was investigated and multiple imputation process was used to manage them. Briefly, we used fully specified chained equations in the R package.19. Five imputed datasets were created and combined using between/within variance techniques to appropriately propagate uncertainty about the missing data[4].

The propensity score was obtained using logistic regression. The variables included in the propensity model were plotted in the supplementary Figure 1. Inverse probability of treatment weighting (IPTW) was obtained for the average treatment effect (ATE). The balance was tested with the standardized mean difference (SMD), which was considered optimal below 0.10. The results were then weighted for IPTW (Figure 1 supplementary).

Early adverse events were analyzed as proportions of the number of patients and described as rates (%). Weighted logistic regression was used as multivariable analysis for early binary outcome. In multivariable models we decided to include, besides different treatment (DHCA+DR vs MHCA+ACP), those operative variables that were not included in the propensity score model (type of arterial cannulation, type of venous cannulation, type of myocardial protection, cardiopulmonary bypass (CPB) duration and nadir temperature reached). ROC curve analysis has been applied to evaluate the correlation between endpoints and variables. All reported p-values were considered statistically significant if below 0.05. R-Studio version 1.1.463 (2009-2018) and SPSS were used for all statistical analyses.

RESULTS

Study population

A total of 210 patients were analyzed. Mean age was 70 years and 35.2% of the patients were female. Fourteen patients (6.7%) had a previous stroke and 33 (15.5%) were in atrial fibrillation. Baseline characteristics are shown in Table 1.

Surgical details are summarized in Table 1. The most common arterial return was through the axillary artery (61.9% of the cases), followed by direct aneurysm cannulation (23.8%), while venous drainage was mainly atriocaval. Associated surgeries were coronary artery bypass grafting in 21.4% of the patients and aortic valve repair/replacement in 49.6%. Mitral and tricuspid valve repair were performed only in 4 cases (1.9%).

Fifty-nine patients (28.1%) underwent DHCA at [?] 20degC without any CP. In 151 cases (71.9%) surgery was performed at moderate hypothermia (26degC) and ACP was obtained through the axillary artery only in 51.7% of the cases, direct cannulation only in 13.9% of the cases while in the remaining 34.4% a mixture of the two methods was used. In 42 cases (27.8%) the left subclavian artery was perfused as well. The median CA time was 24 min, shorter when DHCA (21 min) was used and longer in case of MHCA (26 min) without statistical significance. CA time was >40 min in 19 patients (9%) and >50 min in 11 (5.2%), without any difference when deep or moderately hypotermic CA was used.

Total arch replacement was performed in 103 cases (49%) and ascending aorta with hemiarch replacement in the remaining 107 (51%). An elephant trunk was performed in 61 patients (29%), conventional in 4 (1.9%) and frozen in 57 (27.1%). Median CPB time was 150 min and was not affected by the temperature of the CA. Modality of rewarming after CA were different. In all patients who underwent DHCA rewarming was delayed for a period of 10 minutes, with perfusate temperature at 20degC[1,2]. Patients undergoing MHCA were rewarmed as soon as the perfusion restarted.

Postoperative outcome (Table 2)

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Primary endpoints. Operative mortality included 14 patients (6.7%), who died for cardiac (n=5, 2.4%) and non-cardiac (n=9, 4.3%) causes. NEs occurred in 17 patients (8.1%), stroke in 14 (6.7%) and seizures in 3 (1.4%). NEs symptoms were temporary in 7 patients (3.3%) and permanent in 10 (4.8%). The aggregate endpoint of death+PND were present in 21 patients (10%). Renal function, measured with the KDIGO criteria[3], worsened in 81 patients (38.6%) and need of RRT occurred in 23 (10.9%). Mortality increased with the KDIGO score: 0 1.6% (2/129), 1 5.6% (2/35), 2 19.2% (5/26) and 3 25% (5/20), p=0.001. The composite primary endpoint of death, PND and RRT was observed in 35 patients (19.2%).

Secondary endpoints and other results. Time to extubation was 800 min. Seventeen patients (8.1%) needed tracheostomy and median ICU LOS was 3 days. Seventy-one patients (38.8%) were not transfused and 14 patients (6.7%) were reoperated on for bleeding.

Unweighed groups analysis

Table 1 shows the baseline characteristics of the two groups and the perioperative data. Patients in DHCA+DR group had higher prevalence of diabetes, higher EuroScore II and lower ejection fraction. Total arch replacement and use of frozen elephant trunk (FET) were more frequent in MHCA+ACP. On the contrary aortic valve and mitral surgery were more frequent in DHCA+DR group. CPB time did not differ between groups, but aortic cross clamping time was longer in DHCA+DR group. CA duration was similar in both groups.

Primary endpoints (Table 2). After a median of 14 days (7-34) 14 patients (6.7%) died, 1 (1.7%) in the DHCA+DR group and 13 (8.6%) in MHCA+ACP group, without difference between groups. Causes of death were cardiac in 5 patients and non-cardiac in 9.

NEs prevalence was lower in DHCA+DR group (1.7% versus 10.6%, p=0.034). When only PNDs were considered, there was no difference between the groups (1.7% versus 6%, p=0.193). When ACP was performed, NEs rate was lower when UCP was associated to LCA perfusion, with/our LSA (isolated UCP 16.5%, 12/63, versus 5.1%, 4/78, p=0.025), but PNDs were not different (isolated UCP 8.2%, 6/63, versus 3.8%, 3/78, p=0.258). Seven out of 10 PNDs were embolic of origin, 1 in DHCA+DR and 6 in MHCA+ACP. Death+PND occurred in 21 patients (10%), 2 (3.4%) in DHCA+DR group and 19 (12.6%) in MHCA+ACP group, p=0.046.

KDIGO score was 0 in 83.1% of patients in DHCA+DR group versus 53% in MHCA+ACP (p<0.001). RTT prevalence was higher in MHCA+ACP, 15.2% versus 0, p=0.001. ROC curve analysis showed that, in MHDA+ACP group, RRT was correlated to CA time (cut point 29 min, AUC 0.685, p=0.003) and to CPB time (cut point 127 min, AUC 0.635, p=0.020).

The composite primary endpoint occurred in 3.4% and 21.9% of the patients in DHCA+DR and in MHCA+ACP groups, respectively, p=0.001.

Patients with NEs and need of RRT had higher mortality: 23.5% (4/17, p=0.004) in case of any NE, 30% (3/10, p=0.002) in case of PND and 37.5% (9/24, p=<0.001) in case of RRT.

Secondary endpoints and other results . (Table 2) Time to extubation (590 min versus 938 min, p<0.001) was shorter in DHCA+DR group, as well as ICU LOS (2 versus 4 days, p<0.001), while tracheostomy prevalence was higher in MHCA+ACP (11.3% versus 0, p=0.007). Table 1 supplement shows that time to extubation and ICU LOS remained significantly lower in the DHCA+DR even in patients without composite primary endpoint. Twenty-four-hour bleeding was similar in both groups, but need of transfusion was higher in MHCA+ACP group. It is worthwhile to say that 11.9% of patients in DHCA+DR group and 22.6% in DHCA+ACP group transfused a single unit of blood. In-hospital LOS was similar in both groups.

Weighed logistic regression analysis .

Table 3 compares the risk factors for the primary endpoints, isolated or aggregate, by means of weighed logistic regression analysis. There was no difference between groups in the prevalence of death, any NE and the aggregate of death+PND. On the other side, need of RRT was significantly lower in DHCA+DR

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groups, as well as the composite primary endpoint. The upper confidence limits were anyway high for all the endpoints due to the non-uniform prevalence of the events explored in the analysis.

DISCUSSION

The major finding of this study is that DHCA+DR has the same prevalence of operative mortality, NEs (any or permanent) and association of death+PND than MHCA+ACP. On the other side, lower body protection, evaluated by need of RRT, is significantly better with DHCA+DR. Furthermore, the composite endpoint (death, PND and RRT need) is significantly lower in patients where arch surgery has been performed with DHCA+DR. CPB time and CA time were similar in both groups.

NEs prevalence during aortic arch surgery remains not negligeable and is highly variable in different studies. A report from STS[5] analyzed the cerebral outcome in chronic aortic arch surgery (CA time 25.8 min, T 21.1degC) according to any CP or no CP. PND rate was 6.3%, 7.6% without CP, 6.2% with ACP and 4.6% with RCP ($p<0.001$), favoring any CP. The relationship between temperature and stroke rate has also been widely studied. Urbanski et al[6] in 1000 patients who underwent chronic aortic arch surgery (T 31.1degC, rectal, CA time 18.4 min, all UCP) reported a PND rate of 1% and TND rate of 4.9%. A similar experience was reported by Jabagi et al[7]: in 66 patients with hemiarch replacement (86% elective, T 32degC, CA time 17 min) PND rate was 2% and TND rate 3%. Damberg et al[8] in 613 patients (86.3% elective, CA time 29.7 min, T 18-20 degC) reported a stroke rate of 2% without any CP.

NEs are generally perceived to be linked to the strategy of cerebral protection applied and ACP is considered the safest technique of cerebral protection, but both concepts are not completely true. The great majority of stroke is due to embolism[9-11], which arises from atherosclerosis or thrombi at sites of ascending aorta, aortic arch, aortic arch branches, aortic clamping, vascular anastomosis, and aortic or CP cannulation[10]. ACP allows continuous CP throughout MHCA; however, the manipulation of arch branch vessels, such as dissecting and clamping the arch branch vessels or directly cannulating the ostia of the arch branch vessels, could dislodge debris from the vessels or introduce air into the cerebral circulation, causing cerebral embolism.

DHCA+DR combines different benefits. The epiaortic vessels are not dissected and/or clamped, the aortic arch is not manipulated and no cannula is inserted blindly inside the cerebral vessels. The brain protection is enhanced by DR, that can be defined a cerebral protection after CA. The rationale can be summarized as follows. Glucose is the fuel of the brain and comes from the blood by crossing the blood–brain barrier (BBB). Even if neurons have the capacity to take up glucose directly, due to the specific anatomy of the BBB (astrocytes are in direct contact with BBB, while neurons are not so close) a good part of the glucose that enters the brain does so through astrocytes[12,13] (Fig. 1), from where it can be shuttled to neurons in the form of lactate that, after being converted into pyruvate, enters the Krebs cycle. Oligodendrocytes can transport lactates[14], produced by themselves or by astrocytes, or glucose, if necessary, to neurons through the myelin (Fig. 1). Astrocytes have the possibility as well to store glucose as glycogen, a fuel reserve for the brain metabolism when glucose uptake is reduced or in stress condition.

The metabolic interdependence among neurons, astrocytes and oligodendrocytes allows the neurons to be supported by different energetic sources. This interdependence becomes more important with respect to metabolism of glutamate, the main neurotransmitter in the adult central nervous system, released into the synaptic cleft in a process called exocytosis. Glutamate, after being released, is taken up by surrounding astrocytes, and, after being converted to glutamine, is recycled to neuronal terminals, where it is converted again into glutamate, to replenish the glutamate pool[15-17].

When the glutamate homeostatic balance is disrupted and levels become elevated in the extracellular fluid[18], the excess of glutamate leads to influx of Na+ and Cl– into the postsynaptic cell, causing intracellular hyperosmolarity, and influx of water into the cell, contributing to intracellular oedema and neuronal death (exitotoxicity). Furthermore, glutamate stimulates glutaminergic receptors, but their excessive activation leads to the opening of Ca++ channels. Efflux of Ca++ into neurons, which activates plasmatic proteolytic enzymes, results in neuronal death via apoptosis or necrosis[19-21].

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After circulatory arrest, astrocytes being their glycogen reserve exhausted, cannot send lactate to neurons and cannot maintain low the glutamate level in the extracellular fluid. When the circulation starts again, but the temperature is still low (delayed rewarming), astrocytes use the glucose to rebuild their glycogen stores during a period of time when the metabolism of the neurons is not stimulated by a higher temperature. They start immediately to remove glutamate from the extracellular fluid, eliminating the danger of neuronal death, and to send lactate to neurons to face their metabolic needs. When rewarming starts, metabolic reserves have been restored and the glutamate in the extracellular fluid removed. In general, all organs can benefit from a period of cold perfusion before rewarming, to re-establish their nutrients store.

The progressive increase in the temperature of lower body circulatory arrest reduced the possibility of organs protection, that, in our study, had as target the kidney. Acute kidney injury (AKI) by the KDIGO criteria[3], is common after cardiac surgery (81.2% of the patients: score 1 20.5%, score 2 48.7%, score 3 12%)[22]. In the literature RRT prevalence after CA is variable. Vekstein et al[23] did not find any difference in RRT between DHCA and MHCA. It is likely that RRT need could be related more to CA time rather than to temperature, as it ranges from 7.3%[24] with a CA time of about 23 min to 18%[25] when the mean CA time was 50+-27 min. In our experience any AKI occurred in 38.6% of the patients, 17% in DHCA+DR group and 47% in MHCA+ACP group ($p<0.001$). Deep hypothermia seems to be protective for renal function, especially for RRT need, 0 in DHCA+DR group versus 15.2% in MHCA+ACP, $p=0.001$. In this latter group there was a correlation between CA time and CPB time and RRT need (cut points 29 min and 127 min, respectively), suggesting that, when temperature is higher, longer CA and CPB can affect lower body protection.

Primary endpoints, after weighted logistic regression, failed to show any significant difference between groups, with the exception of RRT need and composite endpoint, both lower in DHCA+DR group. Secondary endpoints were all in favor of DHCA+DR group, in particular time to extubation and ICU time. However, it is possible that these were related to different anesthetic and surgical protocols.

The main limitation of this study is that reflects the experience of several Centers, that used different surgical protocols. Anesthetic techniques were not uniform and outcomes in the postoperative periods can reflect different strategies.

In conclusion, the results of our study demonstrate that DHCA+DR has the same prevalence of operative mortality, NE (any or permanent) and association of death+PND than MHCA+ACP. However, the data seems to suggest that DHCA+DR when compared with MHCA+ACP provides better renal protection and reduced prevalence of composite endpoint. These advantages have to be taken into account when the best surgical strategy has to be chosen for aortic arch surgery

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FIGURE LEGEND

Fig. 1 – Astrocyte-neuron-oligodendrocyte energy metabolism interactions. Glucose in neurons is primarily used for adenosine triphosphate (ATP) production and is metabolized into lactate in astrocytes. The glucose transporters (GLUTs) mediate the transportation of glucose into cells. GLUT1, located in cerebral endothelial cells, transits glucose from the blood into the brain tissue. GLUT1 also mediates the entrance of glucose into astrocytes and oligodendrocytes. Glucose is transported into neurons via GLUT3. Monocarboxylate transporters (MCTs) and connexin (Cx) contribute to astrocyte-neuron-oligodendrocyte lactate transport. MCT1 and MCT4 in astrocytes release lactate, which diffuses into neurons due to the lactate gradient and is actively taken up by neurons via the MCT2. Additionally, MCT1 in the myelin cooperates with MCT2 in the axon to translate the lactate from oligodendrocytes to neurons. Therefore, glucose and lactate, together with their transporters, contribute to the astrocyte-neuron-oligodendrocyte energy metabolism interactions. TCA, tricarboxylic acid; PPP, pentose phosphate pathway; LDH, lactate dehydrogenase. From Zhang et al[26], with permission.

Figure 1 Supplement. Unweighted and weighted standardized mean differences of propensity score model; IPTW = inverse probability of treatment wieghting

Table 1 – Preoperative and perioperative variables.

Variables	Overall	DHCA+DR	MHCA+ACP	p-value
N	210	59	151	
Clinical features				
Age(y)	70(63-75)	69(63-78)	71(64-75)	0.979
Female gender(%)	74(35.2)	15(25.4)	59(39.1)	0.063
Diabetes(%)	21(10)	14(23.7)	7(4.6)	<0.001
Previous stroke(%)	14(6.7)	2(3.4)	12(7.9)	0.247
AF(%)	33(15.5)	11(18.6)	22(14.3)	0.432
EF(%)	60(55-60)	58(54-60)	60(55-60)	0.013
Creatinine (mg/dl)	0.9(0.8-1.1)	0.9(0.8-1.0)	1.0(0.8-1.1)	0.103
Creatinine clearance (mL/min)	86(69-102)	85(69-97)	86(68-104)	0.484
Redo(%)	41(19.5)	8(13.6)	33(21.9)	0.174
EuroSCORE II	3.9(2.4-3.6)	6.2(3.5-9.2)	3.3(2.2-5.5)	<0.001
Surgical details				
Hemiarch replacement(%)	107(51)	44(74.6)	63(41.7)	<0.001
Total arch replacement (%)	103(49)	15(25.4)	88(58.3)	<0.001
FET(%)	57(27.1)	0(0)	57(37.7)	<0.001
ET(%)	4(1.9)	3(5.1)	1(0.7)	0.036
AV surgery(%)	104(49.6)	44(74.6)	60(39.7)	<0.001
Repair(%)	10(4.7)	2(3.4)	8(5.2)	
Replacement(%)	96(45.1)	42(71.2)	54(35.1)	
Bentall(%)	24(23.1)	14(33.3)	10(18.5)	
MV repair(%)	4(1.9)	3(5.1)	1(0.7)	0.036
TV repair(%)	4(1.9)	2(3.4)	2(1.3)	0.326
CABG(%)	45(21.4)	14(23.7)	31(20.5)	0.612
Arterial cannulation				<0.001

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Surgical details				
Femoral	23(11)	6(10.2)	17(11.3)	
Axillary	130(61.9)	9(15.3)	121(80.1)	
Aneurysm	50(23.8)	44(74.6)	6(4)	
Other	7(3.3)	0(0)	7(4.6)	
Venous cannulation				0.021
Atriocaval	181(86.2)	53(89.8)	128(84.8)	
Bicaval	4(1.9)	3(5.1)	1(0.7)	
Femoral	25(11.9)	3(5.1)	22(14.6)	
CPB time (min)	150(125-185)	157(136-184)	144(121-185)	0.132
Aortic clamp time (min)	89(63-117)	119(103-147)	71(57-100)	<0.001
Myocardial protection				<0.001
Isothermic blood	61(29)	59(100)	2(1.3)	
Cold blood	106(50.5)	0	106(50.5)	
HTK solution	43(20.5)	0	43(20.5)	
CA time (min)	24(19-32)	21(19-24)	26(18-33)	
Core temperature(°C)	26(20-26)	20(20-20)	26(26-26)	
Cerebral Protection				
None	59(28.1)	59(100)	0	
Antegrade	151(71.9)	0	151(100)	
UCP only	78(37.1)	0	78(51.7)	
Direct+UCP	52(24.8)	0	52(34.4)	
Direct only LSA perfusion	21(10) 42(20)	0 0	21(13.9) 42(27.8%)	
Duration ACP (min)	...	....	26(16-33)	

Legend. AF = atrial fibrillation, EF =ejection fraction, FET = frozen elephant trunk, ET = elephant trunk, AV aortic valve, MV = mitral valve, TV =tricuspid valve, CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass, HTK = Histidine-Tryptophan-Ketoglutarate, CA = circulatory arrest, UCP = unilateral cerebral perfusion, LCA = left carotid artery, LSA = left subclavian artery, ACP antegrade cerebral perfusion.

Table 2 – Postoperative outcome.

Variables	Overall	DHCA+DR	MHCA+ACP	p-value
	n=210	n=59	n=151	
Primary endpoints				
Death	14(6.7)	1(1.7)	13(8.6)	0.072
Neurologic events	17(8.1)	1(1.7)	16(10.6)	0.034
Type of NE				0.036
Stroke	14(6.7)	1(1.7)	13(8.6)	
Seizures	3(1.4)	0	3(2)	
NE symptoms				0.094
Temporary	7(3.3)	0	7(4.5)	
Permanent	10(4.8)	1(1.7)	9(6)	
NE timing				0.010
Early	16(7.6)	0	16(10.6)	

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Variables	Overall	DHCA+DR	MHCA+ACP	p-value
Delayed	1(0.5)	1(1.7)	0	
Death and/or PNDs Composite primary endpoints§	21(10) 35(19.2)	2(3.4) 2(3.4)	19(12.6) 33(21.9)	0.046 0.001
Secondary endpoints				
Time to extubation (min)	800(460-1185)	590(360-892)	938(523-1445)	<0.001
Tracheostomy	17(8.1)	0(0)	17(11.3)	0.007
ICU LOS	3(2-7)	2(1-3)	4(2-10)	<0.001
Other results				
Confusion	6(2.9)	0	6(4)	0.121
Bleeding 24h (ml)	590(460-800)	540(442-700)	600(460-835)	0.051
Blood transfusion				<0.001
No	71(38.8)	37(62.7)	41(27.2)	
Yes	129 (61.2)	22(37.3)	110(72.8)	
Blood units	1(0-3)	0(0-1.8)	1.5(0-3)	<0.001
Redo bleeding	14(6.7)	3(5.1)	11(7.3)	0.567
Creatinine (peak value, mg/dl)	1.3(1-1.9)	1.1(0.9-1.5)	1.4(1.1-2.1)	<0.001 <0.001
KDIGO score				
0	129(61.4)	49(83.1)	80(53)	
1	35(16.7)	8(13.6)	27(17.9)	
2	26(12.4)	2(3.4)	24(15.9)	
3	20(9.5)	0(0)	20(13.2)	
In-hospital LOS	14(8-24)	11(8-18)	14(8-25)	0.127

Legend. DHCA, deep hypothermic circulatory arrest; DR, delayed rewarming; MHCA, moderately hypothermic circulatory arrest; ACP, antegrade cerebral perfusion; NE, neurologic event; ND, neurological deficit; RRT, renal replacement therapy; ICU, intensive care unit; LOS, length of stay; KDIGO, Kidney Disease: Improving Global Outcome.

Table 3 – Endpoints in the two groups: weighed logistic regression.

Endpoints DHCA+DR MHCA+ACP p WLR

Death 1(1.7) 13(8.6) 0.072 5.46(0.7-42.7)

Any NE 1(1.7) 16(10.6) 0.034 4.65(0.89-53.0)

PND 1(1.7) 9(5.9) 0.089 4.22(0.44-28.9)

Death and PND 2(3.4) 19(12.5) 0.046 8.98(0.90-36.2)

Need of RRT 0 23(15.2) 0.001 7.39(1.37-79.1)

Composite[a] 2(3.4) 33(24.9) 0.001 8.97(1.95-35.3)

Legend. DHCA, deep hypothermic circulatory arrest; DR, delayed rewarming; MHCA, moderately hypothermic circulatory arrest; ACP, antegrade cerebral perfusion; WLR, weighed logistic regression; PND, permanent neurologic deficit; RRT, renal replacement therapy.

[a]Death, PND and RRT

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Table 1 supplement – Secondary endpoints in patients without composite primary endpoint.

DHCA+DR MHCA+ACP p

n=57 n=118

Time to extubation (min) 590(356-878) 720(431-1255) 0.007

Tracheostomy 0 4(3.4) 0.105

ICU LOS (days) 2(1-3) 3(2-6) <0.001

Legend. DHCA, deep hypothermic circulatory arrest; DR, delayed rewarming; MHCA, moderately hypothermic circulatory arrest; ACP, antegrade cerebral perfusion; ICU, intensive care unit; LOS, length of stay.