Medical University - Pleven

Faculty of Medicine

Department of Surgical Diseases

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CEREBRAL PROTECTION IN SURGERY FOR ACUTE TYPE A AORTIC DISSECTION

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Author's Abstract

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The doctoral candidate has been working at the Department of Cardiac Surgery at St. Anna University Hospital, Sofia.

The candidate has been enrolled as a part-time doctoral student at the Department of Surgical Diseases at the Faculty of Medicine of Medical University – Pleven on the grounds of Order №2947/27.11.2018 of the Rector of the University.

The candidate has been discharged with a right of defense on the grounds of Order №1566/05.06.2023 of the Rector of the University.

The dissertation has been considered and referred for public defense at an extended council of the Department of Surgical Diseases on the grounds of Art. 24, par. 6 and Art. 30, par. 3 of the Act for the Development of the Academic Staff in the Republic of Bulgaria and Art. 39, par. 1 of the Rules for the development of the academic staff at the Medical University of Pleven in connection with Decision of Academic Council (Protocol № 2/06.07.2023).

The dissertation consists of 228 typed pages and is illustrated with 41 figures and 22 tables. The list of cited literature consists of 526 articles in English.

The public defense of the dissertation will take place on the 26th of October 2023 at 14:00 h in Ambroise Pare Hall, Telecommunication Endoscopic Centre of the Medical University of Pleven on the grounds of Order №2106 from 25.07.2023 by Prof. Dobromir Dimitrov Dimitrov, MD, PhD, Rector of the University, in front of a scientific jury in the following composition:

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The defense materials are at disposal at the Department of Science of the Medical University of Pleven and are uploaded at the university website *http://mu-pleven.bg*.

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List of abbreviations

AAAD – acute type A aortic dissection

AAD – acute aortic dissection

ACP – antegrade cerebral perfusion

ARDS – acute respiratory distress syndrome

bACP – bilateral antegrade cerebral perfusion

BMI – body mass index

CABG – coronary artery bypass grafting

CPB – cardiopulmonary bypass

CPR – cardiopulmonary resuscitation

CT – computed tomography

CVD – cerebral vascular disease

FFP – fresh frozen plasma

HCA – hypothermic circulatory arrest

IABP – intraaortic balloon pump

ICU – intensive care unit

IHD – ischemic heart disease

iqr – interquartile range

IRAD – International Registry of Acute Aortic Dissection

OR – odds ratio

PND – permanent neurologic dysfunction

RBCs – red blood cells

RCP – retrograde cerebral perfusion

SIRS – systemic inflammatory response syndrome

STS – Society of Thoracic Surgeons

TEE – transesophageal echocardiography

TND – transient neurologic dysfunction

TRALI – transfusion-related acute lung injury

I. INTRODUCTION.

Cardiac surgery is characterized by high levels of invasion into the structure and physiological processes of the human body. Nearly all cardiac surgical procedures are carried out by means of extracorporeal circulation which allows intervention upon the delicate structures of the heart. Manipulation of heart structures in the setting of non-physiologic blood circulation may cause various side effects sometimes escalating into clinically important complications. Neurologic complications are frequent after open heart surgery. Patients with postoperative neurologic injury often need prolonged hospital stay and exhibit higher mortality. Survivals with postoperative neurologic injury have impaired quality of life and lower long-term survival. Thus such patients present additional financial burden to the health care and social systems.

Acute aortic dissection (AAD) is one the most critical conditions in medicine and nearly always mandates emergent surgery. The incidence of AAD is increasing over the past two decades due to heightened awareness and better diagnostic technology. The surgical treatment of AAD is an aggressive interference to the human body that along with the correction of the problem could bring about serious injury to the patient. Oftentimes the surgical correction of acute dissection requires cessation of blood circulation, the so called circulatory arrest. The incidence of neurologic complications after AAD surgery is higher than that of general cardiac surgery. That is why efforts are needed to minimized those complications. Over the history of cardiac surgery the methods of cerebral protection undergo smooth evolution. Simple cooling of the brain and body is the first perceived method which has still full meaning today. Different techniques of cerebral perfusion during the period of circulatory arrest were developed throughout the years. The techniques differ on the basis of the direction of blood flow – antegrade versus retrograde, the cannulation strategy for cerebral perfusion, and the laterality – unilateral versus bilateral perfusion. In spite of many clinical and experimental trials there is still no firm answer as to what is the best strategy of cerebral protection.

In the department of cardiac surgery at St. Anna University Hospital the surgical treatment of acute type A aortic dissection (AAAD) involves implementation of hypothermic circulatory arrest (HCA) with bilateral antegrade cerebral perfusion (bACP) in nearly all patients.

This scientific work relies on data obtained entirely from the department of cardiac surgery, St. Anna University Hospital, and gives clarity on the effectiveness and safety of bACP in the present cohort.

II. AIM AND TASKS.

1. Aim.

The aim of the dissertation is evaluation of the effectiveness and safety of hypothermic circulatory arrest with complementary selective antegrade cerebral perfusion for brain protection against ischemia during construction of open distal anastomosis in acute type A aortic dissection surgery.

2. Tasks.

A. Analysis of preoperative, clinical, and demographic characteristics of the patients with acute type A aortic dissection.

B. Analysis of the implemented method of cerebral protection in the present group of patients.

C. Description of the operative techniques used in the present group.

D. Analysis of early postoperative results concerning length of mechanical ventilation, intensive care unit and hospital stays, and important complications stemming from the operative treatment.

E. Analysis of postoperative neurologic morbidity, the role of cerebral protection methods, revealing the causes of its occurrence, and its effect on patient outcomes.

F. Analysis of the early and late postoperative mortality and the its relationship with postoperative neurologic morbidity.

III. MATERIALS AND METHODS.

1. Study design.

The present work is a retrospective observational longitudinal study analyzing the influence of selective antegrade cerebral perfusion in the setting of hypothermic circulatory arrest upon early and later results of operative treatment of acute type A aortic dissection. All patients are separated into two groups – group A (HCA/bACP, therapeutic group) and group B (no HCA/bACP, control

group). Comparative analyses are conducted between the two groups. In HCA/bACP group the distal anastomosis was carried out on the open aorta and in the no HCA/bACP it was carried out on the closed (clamped) aorta. The open distal aortic anastomosis has technical benefits compared to the closed anastomosis. Considering that the HCA has limitations and may cause various complications, achieving similar results between group A and group B can be viewed as a positive result (non-inferior) and points out that ACP negates the adverse effects of HCA. Thus the results of the comparative analysis may promote or limit the choice of open distal anastomosis during surgery for AAD. Patient data was collected from the electronic and paper records of the department of cardiac surgery at St. Anna University Hospital encompassing a period of 13 years (2010-2022). Due to the retrospective nature of the current research patient agreement was not sought but permission of the hospital ethics committee was obtained. Information about live/dead status was extracted from a national database system and the relatives of dead patients were contacted to clarify the moment of death.

2. Inclusion criteria.

The study includes a series of patients operated for AAAD. All patients were offered surgery despite their preoperative state or additional medical conditions. Four patient were set to medical treatment due to comatose state (absence of reflexes and spontaneous breathing) with uninterpretable neurologic status, and were thus not eligible for analysis.

3. Demographic and clinical characteristics.

As usual of all acute medical conditions the patients from the present group had a certain geographic distribution. The majority of patients came from the western part of the country, mainly Sofia City and Sofia Province. The were no patients from the most eastern and southern provinces (fig. 1). There was one patient from the Republic of North Macedonia.

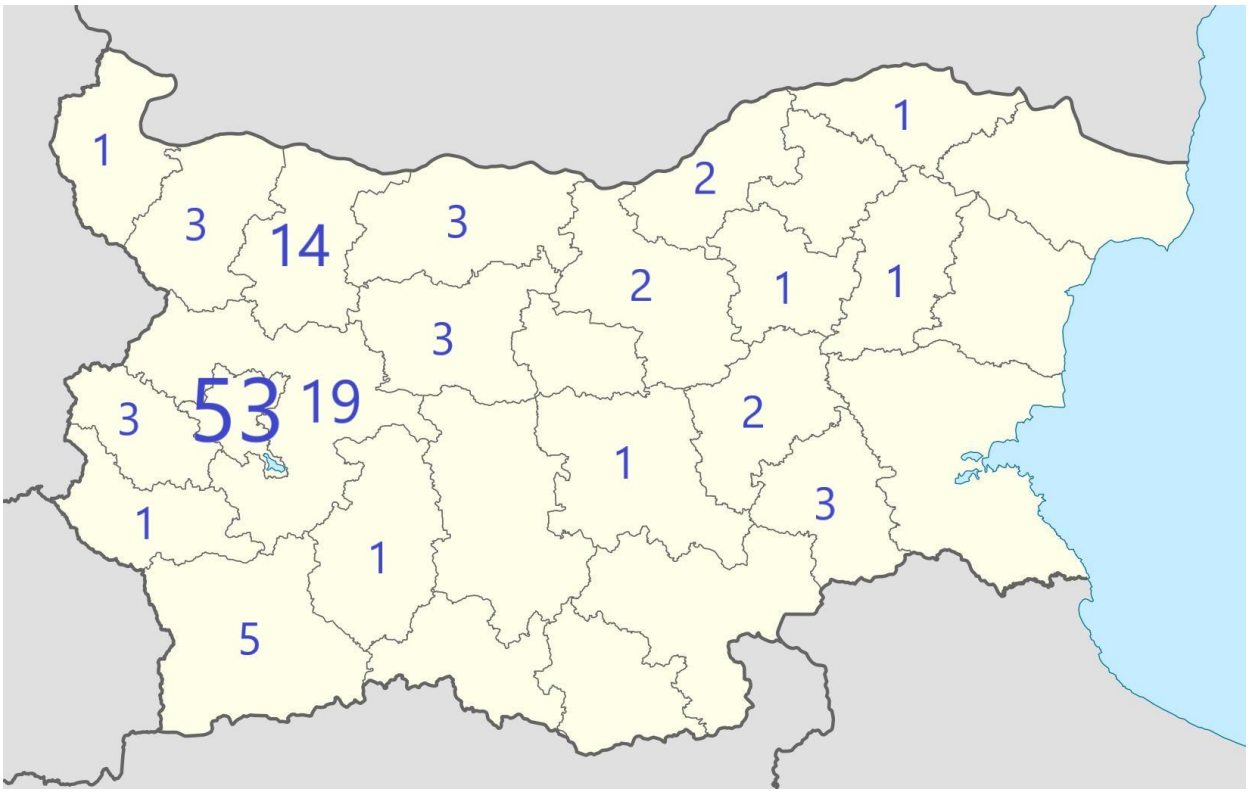

Fig. 1. Origin of patients in terms of geographic provinces.

The study includes 120 patients operated emergently for acute type A aortic dissection over the period of 2010-2022. 87 (72.5%) were male and 33 (37.5%) were female. Mean age was 59±12 years. Mean body mass index was 28.2±5.3 $kg.m^{-2}$ (median 27.2, iqr 24.6-32.0). Mean preoperative hemoglobin was 130.1±19.5 g/L. 93 (77.5%) patients presented with De Bakey type I dissection, 24 (20.0%) with type II, two patients (1.7%) with type III dissection with retrograde involvement of the aortic arch, and one patient (0.8%) with acutely dissected chronic calcified aneurysm of the ascending aorta and arch. 111 patients (92.5%) had a history for arterial hypertension or antihypertensive therapy. 9 patients (7.5%) had been diagnosed with diabetes mellitus. 29 patients (24.2%) had hereditary aortopathy as 17 (14.2%) had bicuspid aortic valves, and 12 (10%) reported family history of aortic aneurysm or dissection. 4 (3.3%) patients suffered from Marfan syndrome. 4 (3.3%) patients had ischemic heart disease, 3 (2.5%) had experienced a myocardial infarction, and 8 (6.7%) presented with acute myocardial ischemia as a result of the dissection process. 7 patients (5.8%) had history of stroke.

At the initial neurologic assessment, which was conducted by the attending surgeon and anesthesiologist, 104 patients (86.7%) did not have any neurologic disturbances. 4 patients (3.3%) demonstrated motor deficit (hemiparesis). 4 patients (3.3%) were in stupor, 5 (4.2%) report syncope before admission, 3 (2.5%) were in hyperactive delirium.

58 (48.3%) patients were hypertensive on admission (systolic blood pressure >140 mmHg or need for vasodilators). 24 patients (20.0%) were hypotensive (systolic blood pressure <120 mmHg). 8 patients were in a shock state (systolic blood pressure <90 mmHg or need for vasoconstrictors). 1 patient was being resuscitated on transfer to the operating room.

9 patients (7.5%) had atrial fibrillation on admission.

75 patients (62.5%) had normal renal function, 26 patients (21.7%) presented with nonoliguric renal failure, 15 patients (12.5%) with oliguric renal failure (urine output <10 ml/h), and 4 patients (3.3%) had chronic renal disease.

Diminished or absent pulse in at least one limb was found in 35 patients (29.2%). 12 patients (10.0%) had symptoms of mesenteric ischemia – abdominal pain on palpation, nausea, vomiting, loss of peristalsis.

Based on echocardiography or computed tomography 50 patients (41.7%) had associated pericardial effusion, 9 of which (7.5%) developed cardiac tamponade. 55 patients (45.8%) had at least moderate aortic regurgitation (grade II or higher). Mean left ventricular ejection fraction was 57±7 %.

The cohort was divided into two groups in order to assess the effectiveness of ACP in AAAD surgery. Group A includes 81 patients (67.5%) operated under HCA/ACP with open distal anastomosis. Group B is a control group and includes 39 patients (32.5%) operated with continued systemic perfusion and closed distal anastomosis. Tables 1 and 2 below show comparative analysis of the measured preoperative characteristics of both groups.

4. Operative approach.

4.1. Surgical goal and techniques.

The goal of surgical treatment of AAAD is resection of the dissected aortic segment which includes intimal entry tear and its replacement with the appropriate vascular prosthesis. The resected

segment is sent for pathologic examination to exclude a degenerative process of the aortic wall. The extent of resection always includes the entire ascending aorta and sometimes part of or the whole aortic arch. The operation mandates cardiopulmonary bypass (CPB) and oftentimes a period of cessation of the systemic circulation, the so called circulatory arrest. In the HCA/ACP group the distal anastomosis is sewn to the "open" and exsanguinated aorta, whereas in the no HCA/ACP group it is done to the rim of aortic wall under the clamp of the "closed" aorta. The anastomosis is carried out with continuous running monofilament suture of non-absorbable polypropylene 3/0 with felt buttress. The proximal aortic anastomosis was performed with the same technique. All suture line are reinforced with fibrin glue. In cases of Bentall procedure or aortic valve replacement the valve prosthesis was implanted with single braided sutures with felt buttresses by a non-everting technique.

Characteristic	Group A (HCA/ACP)	Group B (no HCA/ACP)	*p*
Age	60.3±11.3	57.0±13.6	*0.166*
Gender (male)	59 (72.8%)	28 (71.8%)	*0.904*
BMI $kg.m^{-2}$	28.2±5.5	28.1±5.1	*0.886*
Hemoglobin *g/L*	135.1±17.4	127.6±20.1	***0.049***
De Bakey type			
Type I	72 (88.9%)	21 (53.8%)	***0.000***
Type II	7 (8.6%)	18 (46.2%)	
Type III	2 (2.5%)	0 (0%)	
Arterial hypertension	77 (95.1%)	34 (87.2%)	*0.148*
Diabetes mellitus	5 (6.2%)	4 (10.3%)	*0.47*
Bicuspid aortic valve	8 (9.9%)	9 (23.1%)	*0.052*
Aortopathy			
Non-syndromic aortopathy	13 (16.0%)	16 (41.0%)	***0.004***
Marfan syndrome	2 (2.5%)	2 (5.1%)	

Table 1. Comparative analysis of clinical and demographic data between groups A and B.

Characteristic	Group A (HCA/ACP)	Group B (no HCA/ACP)	*p*
IHD			
Stable angina	2 (2.5%)	2 (5.1%)	
Previous myocardial infarction	3 (3.7%)	0 (0%)	*0.348*
Acute myocardial ischemia	7 (8.6%)	1 (2.6%)	
Previous stroke	6 (7.4%)	1 (2.6%)	*0.425*
Neurologic symptoms			
Motor deficit	2 (2.5%)	2 (5.1%)	
Stupor	3 (3.7%)	1 (2.6%)	*0.207*
Syncope	5 (6.2%)	0 (0%)	
Delirium	3 (3.7%)	0 (0%)	
Hemodynamics			
Hypertension	40 (49.4%)	18 (46.2%)	
Hypotension	19 (23.5%)	5 (12.8%)	*0.238*
Shock	6 (7.4%)	2 (5.1%)	
CPR	1 (1.2%)	0 (0%)	
Unstable hemodynamics	26 (32.1%)	7 (17.9%)	*0.104*
Renal failure			
Chronic	4 (4.9%)	0 (0%)	
Acute non-oliguric	22 (27.2%)	4 (10.3%)	*0.062*
Acute oliguric	10 (12.3%)	5 (12.8%)	
Acute kidney injury	32 (41.6%)	9 (23.1%)	***0.049***
Limb ischemia	25 (30.9%)	10 (25.6%)	*0.555*
Mesenteric ischemia	8 (9.9%)	4 (10.3%)	*1.0*
Pericardial effusion	32 (39.5%)	18 (46.2%)	*0.489*
Tamponade	8 (9.9%)	1 (2.6%)	*0.268*
Aortic regurgitation ≥ II ст.	36 (44.4%)	19 (48.7%)	*0.660*
Ejection fraction	57.4±5.9	57.7±7.6	*0.821*

Table 2. Comparative analysis of the clinical presentation between the two groups.

4.2. Cannulation for CPB.

The operative approach for AAAD surgery was through median sternotomy. Arterial cannulation for CPB was accomplished through the dissected ascending aorta, the so called central cannulation. The cannula used was a peripheral arterial cannula for percutaneous placement - EOPA™ (Elongated One-Piece Arterial), which was introduced by the Seldinger technique (fig. 2 and fig. 3). The insertion was always targeted at true lumen which was checked during and after cannulation by TEE (fig. 4). Venous cannulation was carried out into the right atrium – inferior vena cava by a two-stage cannula. Venous outflow was through passive drainage. A vent was positioned into the left ventricle through the right superior pulmonary vein for de-airing and decompression of the heart at the end of the procedure. Prior to removal of the aortic cross-clamp a vent was placed into the aortic prosthesis to evacuate any entrapped air. Upon cross-clamp removal the common carotid arteries were gently compressed manually over 10 seconds to block entry of any emboli. A standard bypass circuit comprised of membrane oxygenator with integrated 40 μm arterial filter, hardshell reservoir, roller pump head, and non-heparinized surface, was used.

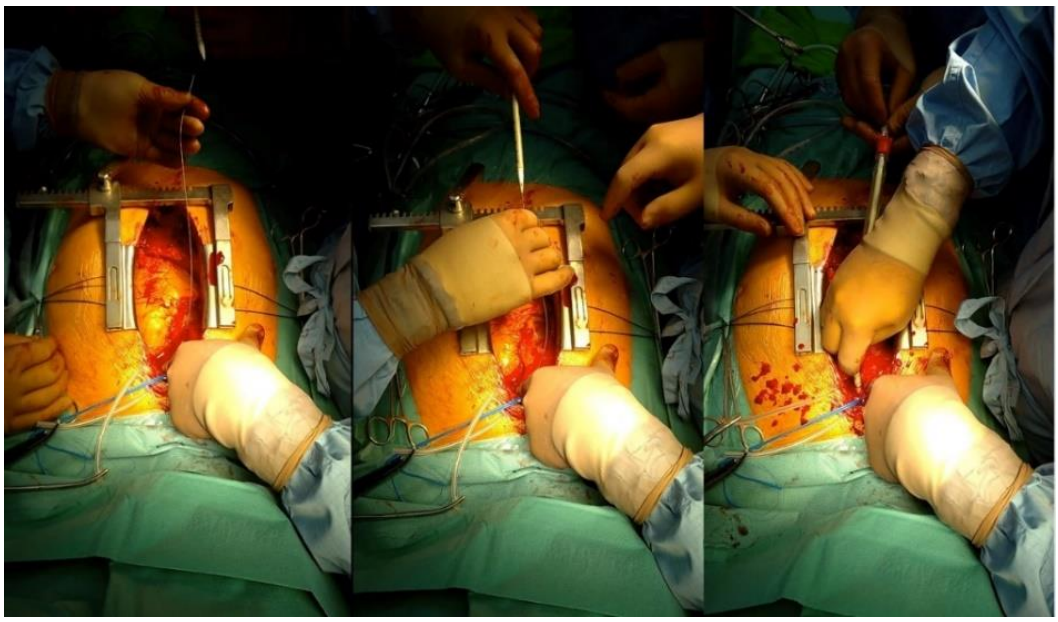

Fig. 2. True-lumen cannulation of the dissected aorta by the Seldinger technique.

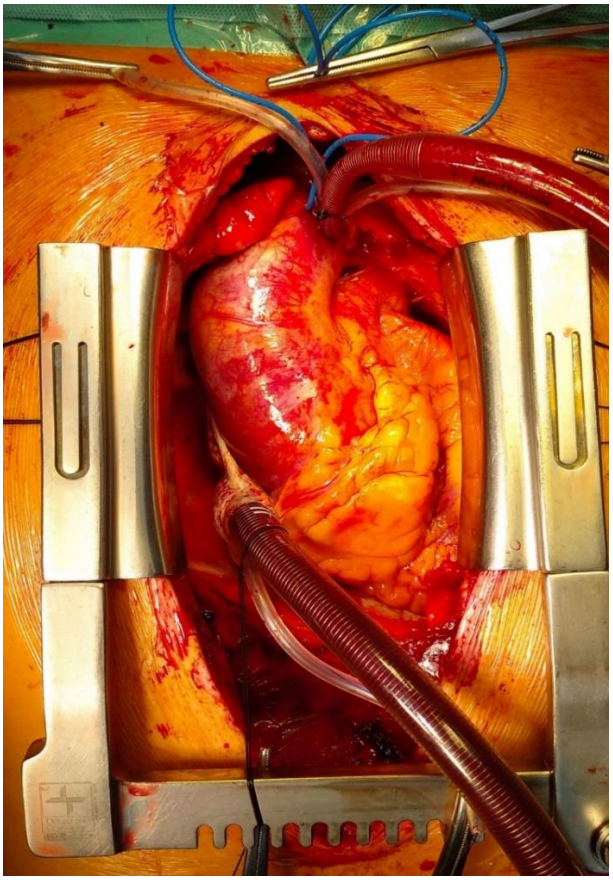

Fig. 3. Final view of the CPB set-up in the present group of patients.

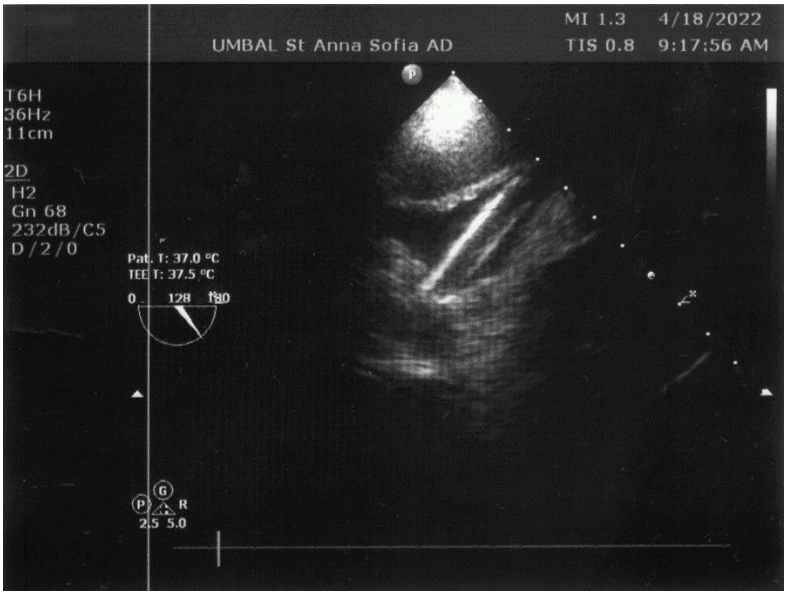

Fig. 4. Intraoperative transesophageal echocardiography verifying the positioning of the arterial cannula in the true aortic lumen.

4.3. Cardiopulmonary bypass and hypothermia.

Targeted CPB flow was 2.2-2.4 $L.min^{-1}.m^{-2}$. Myocardial protection was achieved by a cold crystalloid hyperkalemic solution delivered by special cannulas into the coronary ostia. After CPB initiation core body cooling was commenced to 24-32ºC depending on patient hemodynamics and the expected extent of operation. The heat exchanger cooled the venous blood before its passing through the oxygenator. A gradient was created between the oxygenated and cold blood entering the patients and the warmer tissues. CPB allowed precise and controlled achievement of target body and brain temperatures. During the cooling phase the temperature gradient between the perfusate and rectal temperature did not exceed 10°C. Acid-base management involved the *alpha-stat strategy* which caused progressive alkalosis and hypocapnia along the body cooling. The ascending aorta was crossed-clamped soon after the initiation of CPB. Upon cross-clamping any changes in bilateral radial artery and femoral artery pressures were noted as the may signify compromised true lumen perfusion with risks of organ ischemia. After cross-clamping aortic root and proximal aortic corrections were undertaken. Aortic cross-clamping before the start of HCA does not affect the early postoperative results, the decision-making should be individual [505].

During CPB blood glucose control was achieved by a continuous insulin infusion as the target values were below 10 $mmol.L^{-1}$. The preferential hematocrit during hypothermic CPB was 20-25%.

4.4. Circulatory arrest and antegrade cerebral perfusion.

The distal anastomosis was sewn to the “open” aorta in 81 patients and to the “closed” aorta in 39 patients. The open distal anastomosis was carried out under circulatory arrest and total body hypothermia. Hypothermia was achieved by the controlled cooling of the CPB perfusate as well as drifting the operating room temperature down to 18ºC. Patient temperature was monitored by thermistor probes placed in the rectum and nasopharynx. Rectal temperature corresponds to core body temperature and nasopharyngeal temperature nears the head and brain temperatures. The brain always overtakes the body during cooling and rewarming due to its better developed vascular bed and higher blood flow. When decision was made to implement HCA/ACP ice blocks were placed around the head to enhance brain cooling through convection and prevent its spontaneous rewarming from the surrounding environment. Prior to cessation of circulation the nasopharyngeal temperature was maintained at 25-28°C for 5 minutes, which ensured homogeneous cerebral

cooling. Circulatory arrest was initiated after pharmacologic pretreatment with mannitol 1 $g.kg^{-1}$ in the CPB prime and methylprednisolone 10 $mg.kg^{-1}$ or dexamethasone 80 mg 30 minutes before arrest. In addition to pharmacologic brain protection sodium thiopental was applied in some cases as a continuous infusion at a dose 3 $mg.kg^{-1}$. The HCA was always accompanied by selective perfusion of the brachiocephalic trunk and the left common carotid artery with cold oxygenated blood from a side port of the arterial arm of the CPB circuit (fig.5 and fig.6). these two arteries were perfused by special cannulas for retrograde cardioplegia (fig. 7 and fig. 8). The balloon cannula has a port at its tip which allows continuous cerebral blood pressure monitoring during ACP.

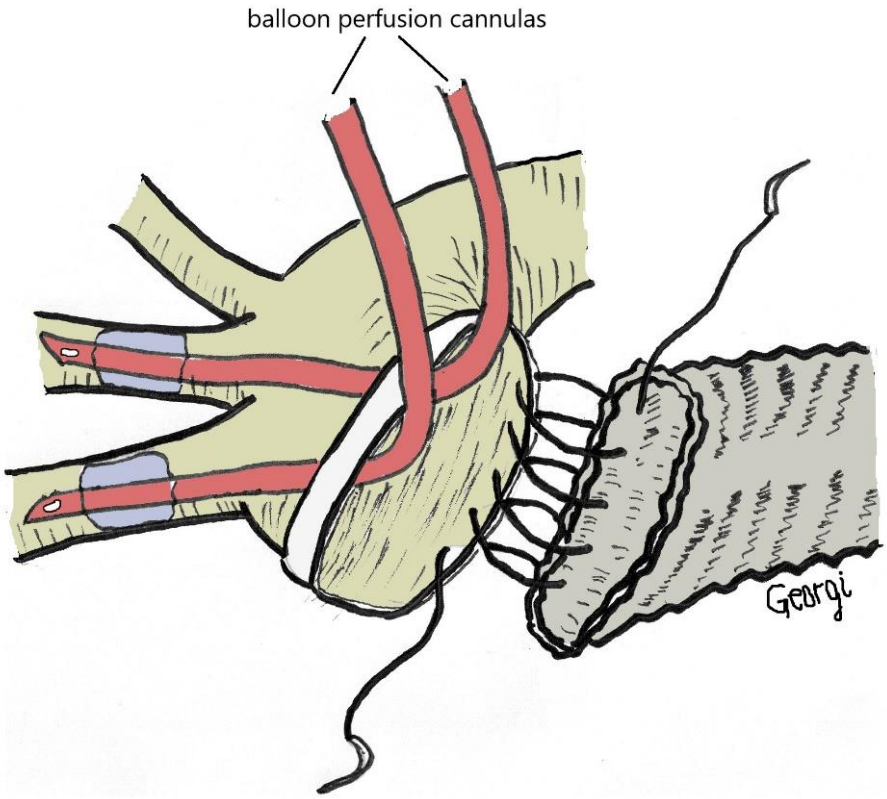

Fig. 5. Transostial cannulation of the brachiocephalic trunk and the left common carotid artery through the open aorta to perform ACP.

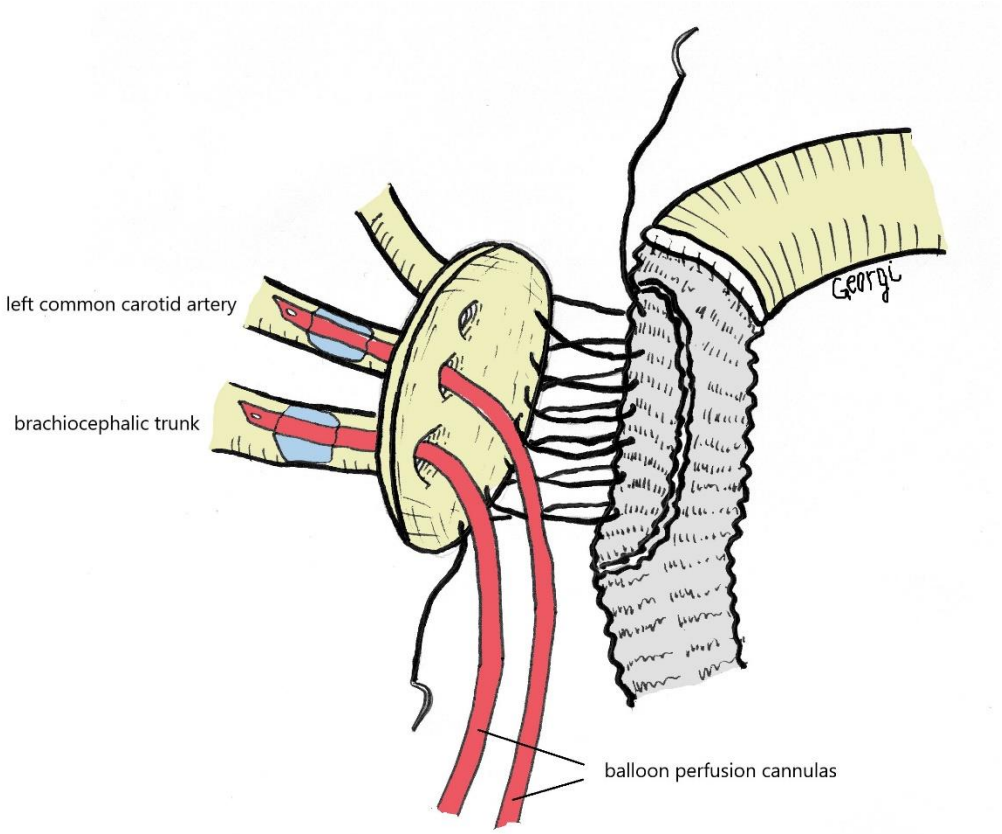

Fig. 6. Transostial cannulation of the arch branches to perform ACP during whole arch replacement.

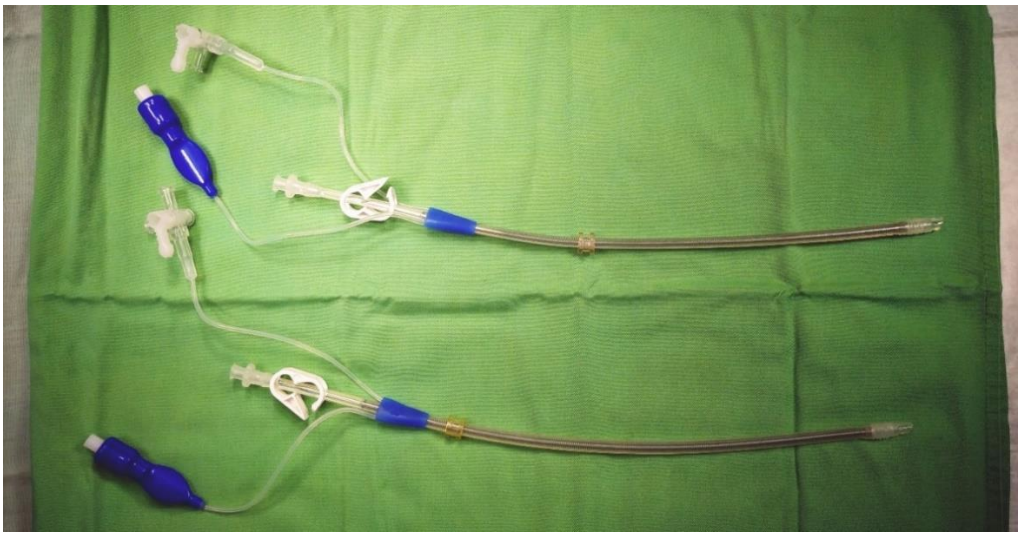

Fig. 7. Balloon-inflated cannula for retrograde cardioplegia utilized for antegrade cerebral perfusion as well.

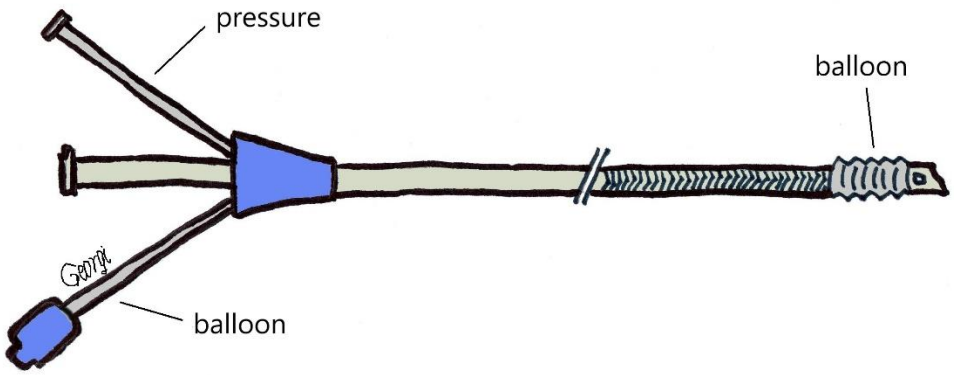

Fig. 8. Diagram of the balloon-inflated cannula.

Just prior to initiation of HCA/ACP the patients was placed in 15-20º head-down (Trendelenburg) position. Systemic perfusion was stopped, the aortic cross-clamp removed and the aorta exsanguinated. The brachiocephalic trunk and the left common carotid artery were identified and cannulated. As blood flow through the cannulas was started the arch vessel were deaired and the occluding balloons inflated with serum. The setup of ACP takes about half a minute of cerebral circulatory arrest. Accepted perfusion flows were in the range of 500 to 800 ml.min^{-1} (6-10 ml.kg^{-1}.min^{-1}) at 24-28ºC perfusate temperature and target cerebral arterial pressures 60-80 mmHg. Correlation between blood flow and perfusion pressure was different in individual patients as the flow was adapted to achieve a target pressure. The backflow of blood through the left subclavian artery was a sign of good collateralization of the posterior cerebral circulation through the Willis circle. When backbleeding was significant the ostium of the subclavian artery was occluded with Fogarty catheter to prevent steal-phenomenon and improve operative visibility.

4.5. Reperfusion conditions.

After distal aortic repair was completed the ACP was stopped, balloon cannulas removed, the aortic prosthesis was cannulated and clamped, and systemic perfusion resumed. Patient was positioned head-down 15-20º (Trendelenburg) as the anesthesia team manually compresses the common carotid arteries for 10 seconds. This maneuver prevents air and particulate embolism into the arch vessels. The whole act involves a cerebral circulatory arrest of approximately half a minute. The corporeal reperfusion flow was 2.2-2.4 L.min^{-1}.m^{-2} with perfusate temperature of 24-28ºC for 5 minutes (or equivalent to nasopharyngeal temperature). Then patient rewarming

followed with temperature gradient between the perfusate and rectal temperature no higher than 6°C. The maximal temperature of the perfusate was 37°C, which protects the delicate blood components from injury. Rewarming was discontinued at a nasopharyngeal temperature of 36.5°C, which salvages the brain from hyperthermia. The body was being reperfused for 15 minutes at target temperature before termination of CPB. Thus homogeneous brain rewarming was aimed. Reperfusion was marked by the alpha-stat control of the acid-base management. Hematocrit was maintained between 25 and 30%. Blood glucose levels were preferably below 10 $mmol.L^{-1}$.

5. Outcome measures.

The effectiveness of bilateral ACP as a method of cerebral protection was assessed through a comparative analysis between the two separate groups – the "open aorta" group (with HCA/ACP) and the "closed aorta" (no HCA/ACP). The valuation was completed by summarizing and comparing the following outcome measures:

5.1. Operative (hospital) mortality and 24-hour mortality. Long-term survival.

The operative mortality was defined as any-cause death during the index hospital stay or up to 30 days following the operative treatment. The 24-hour mortality was death occurring until the end of the first postoperative day (hyperacute phase) and it was considered to have been entirely due to intraoperative events. The long-term survival demonstrated the probability for a given patient to be alive after a certain period of time.

5.2. Permanent neurologic deficit (PND)/stroke.

PND is defined as an acute episode (duration >24 hours with incomplete resolution of symptoms upon discharge) of focal or global neurologic deficit which includes hemiparesis/ hemiplegia, loss of sensitivity of one side of the body, dysphasia/aphasia, hemianopsia with corresponding findings on imaging studies; also, neurologic incidence causing patient's death. Patients with coma were accounted for separately.

5.3. Temporary neurologic dysfunction (TND).

TND represents qualitative or quantitative alterations in consciousness which are completely reversible upon patient's discharge. It is also called acute psychosis or delirium. TND includes transitory ischemic attacks which are defined as a focal motor or sensory deficit with duration <24

hours, and complete resolution of symptoms. Late awakening of patients from anesthesia in the absence of other causes was viewed as a TND and was described separately. Late awakening was marked when a patient did not regain contact and spontaneous breathing at least 24 hours after the end of operation without any sedation.

5.4. Secondary outcome measure.

5.4.1. Acute heart failure.

It is defined as postoperative heart failure necessitating prolonged inotropic support (>24 hours) or the implantation of mechanical circulatory support device to prevent end-organ dysfunction. In neurologically intact patients the development of acute heart failure may increase the operative mortality.

5.4.2. Intensive care unit and hospital stay. Duration of mechanical ventilation. Postoperative lung injury.

The stay in the intensive care unit was determined by the patient's need for mechanical ventilation and monitoring of vital parameters. Between-group differences were assessed as they influence operative mortality.

5.4.3. Postoperative blood loss, blood product transfusion, and reoperation for bleeding.

Reoperation for bleeding was reopening of the chest in the intensive care unit or operating room for excessive ongoing bleeding. Reoperation for bleeding and the increased use of blood products raise the operative mortality and may confound the effect of neurologic dysfunction on the same parameter.

5.4.4. Assessment of key postoperative laboratory results.

Such laboratory parameters were hemoglobin, creatinine and lactate, which were related to the hemodynamic state of the patient, tissue metabolism, and therefore the primary outcomes - operative mortality and neurologic morbidity.

5.4.5. Systemic inflammatory complications.

Systemic inflammatory complications represent generalized inflammatory process triggered by activation of the complement, kinin-kallikrein system, and the coagulation cascade. They can be

differentiated into infectious systemic inflammation (*sepsis*) and noninfectious systemic inflammatory response syndrome (*SIRS*). Both forms of systemic inflammation raise the operative mortality and neurologic morbidity.

6. Assessment of postoperative neurologic function.

The initial assessment of any postoperative neurologic dysfunction was performed by the operating surgeon after the patient came out of anesthesia or immediately after extubation. If deviation from normal function was noted, a neurologist was called. The main neurologic symptoms sought were late awakening, qualitative or quantitative disturbances in consciousness, motor deficits. Should any doubt about stroke arise, a contrast-enhanced computed tomography was performed 24 hours after symptom onset.

7. Statistical analysis.

The statistical workup of all data was performed by the software package SPSS v.26.0 (IBM Corporation, Armonk, NY, USA). Standard statistical methods were used:

7.1. Descriptive statistics.

Metric variables (continuous or interval) were summarized as means and standard deviation or median and interquartile range. Parameters with normal or close to normal distribution were presented as mean ± standard deviation. The coefficient of skewness was calculated in quantitative variables. In case it was higher than 1 or lower than -1, the respective variables were presented as median and interquartile range, minimum and maximum value. The categorical variables were summarized with absolute and relative frequency (percent). All outliers of metric variables were identified and excluded from further analysis due to significant effect on asymmetry of distribution. Values with a Z-score higher than 3.0 were regarded as outliers.

Graphic images were created and include histograms, boxplots, and bar charts. Histograms help assess the asymmetry of distribution.

7.2. Analytical methods.

The analytical method are based on the formation of null hypothesis (H_0), which is rejected if the *p* value is lower than 0.05. If $p > 0.05$ the probability of type 1 error (rejection of H_0 when it is true) is large and therefore H_0 is accepted. When H_0 is accepted we assume that there is no

statistically significant difference between the two variables in the population which is represented by the patient sample.

Parametric methods. The parametric methods are appropriate for metric variables with normal or near-normal distribution. Student's t-test compares the means of the variables between two independent samples. The one-way ANOVA dispersion analysis was used to compare the distribution of a certain variable between more than two independent samples.

Nonparametric methods. All metric variables were tested for normal distribution by the Kolmogorov-Smirnov and the Shapiro-Wilk tests. The Mann-Whitney U-test was used to compare the medians of two independent samples with asymmetric distribution. The categorical variables were entered into cross-tabulations and their interdependence was assessed through chi-square test and the Fischer's exact test where appropriate.

Correlation. The correlation analysis was used to check the strength and type of association between two metric variables. Pearson's correlation coefficient (r) measures the linear association of two metric continuous variables that are normally distributed.

Regression. Binary logistic regression was used to determine any independent predictors of adverse outcome. Odds ratio with 95% confidence interval was calculated. Initially each probable predictor was individually regressed and then included in the multivariable logistic regression model with the forward stepwise elimination method. Thus the simultaneous effect of all probable predictors was assessed and confounding was limited. The coefficient of determination R^2 was calculated as well.

The influence of the main predictor (intervention) on the adverse outcome was controlled by the propensity score adjustment through selected variables which have effect on the predictor. The propensity score showed the probability of one patient belonging to one or the other group.

Survival. Long-term survival was assessed by Kaplan-Meier analysis. This method showed the probability of a patient being alive after a certain amount of time following discharge from hospital. A log-rank (Mantel-Cox) test was applied to find any statistically significant difference in survival function between groups. Cox-regression analysis was performed to assess the predictor

value of HCA/ACP and postoperative neurologic dysfunction on long-term survival. Survival plots were formed.

VI. RESULTS.

The following time chart demonstrates the yearly frequency of AAAD in the department of cardiac surgery for the study period. The mean number of operations for AAAD was 9.2 per year (fig. 9).

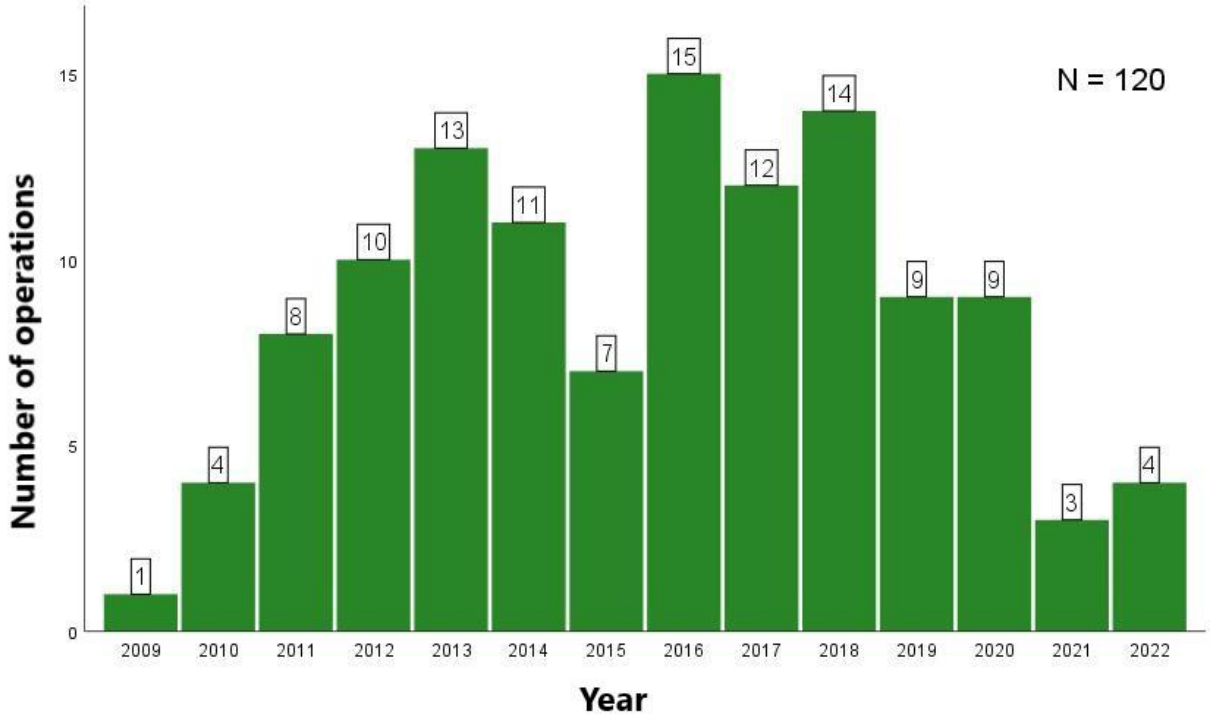

Fig. 9. Yearly rate of operations for AAAD.

1. Summary of the intraoperative and early postoperative results and comparative analysis between group A and group B.

1.1. Data of HCA/ACP (group A).

81 patients underwent hypothermic circulatory arrest with adjunctive antegrade cerebral perfusion with open distal aortic anastomosis. 39 patients did not undergo HCA/ACP and the distal aortic anastomosis was done on a clamped aorta and continual body perfusion. Figures 10 through 17 illustrate the distribution of results of various parameters of HCA/ACP (group A).

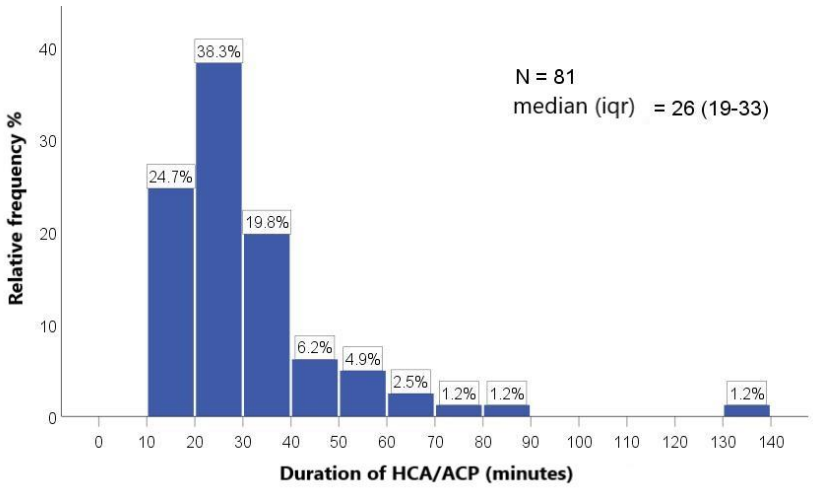

Fig. 10. Histogram of the duration of HCA/ACP in group A.

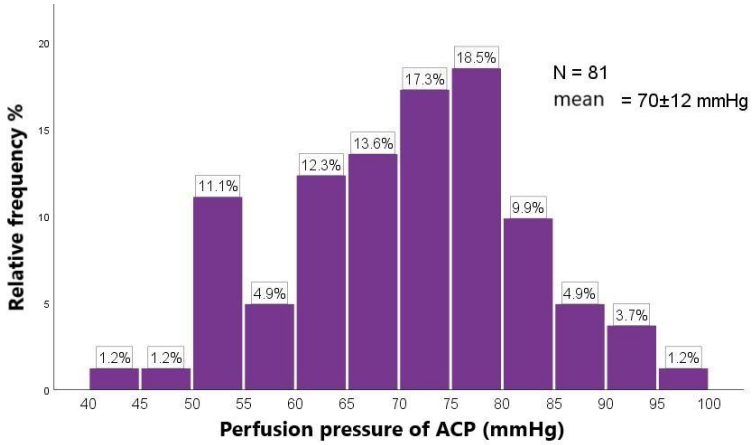

Fig. 11. Histogram of the perfusion pressure of HCA/ACP in group A.

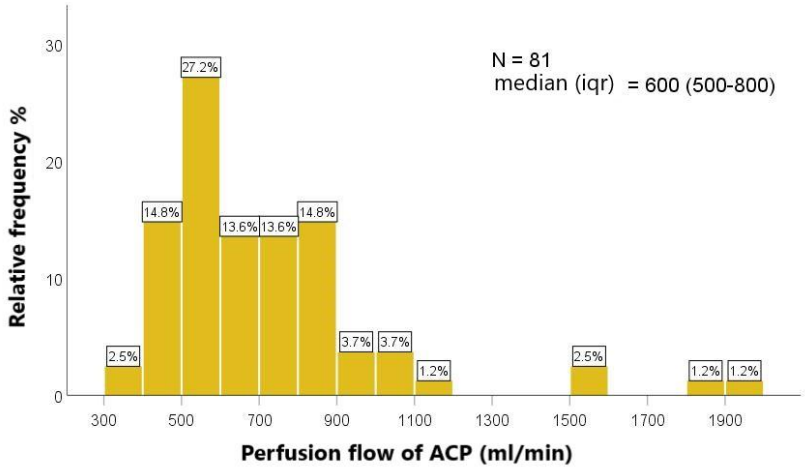

Fig. 12. Histogram of the perfusion flow of HCA/ACP in group A.

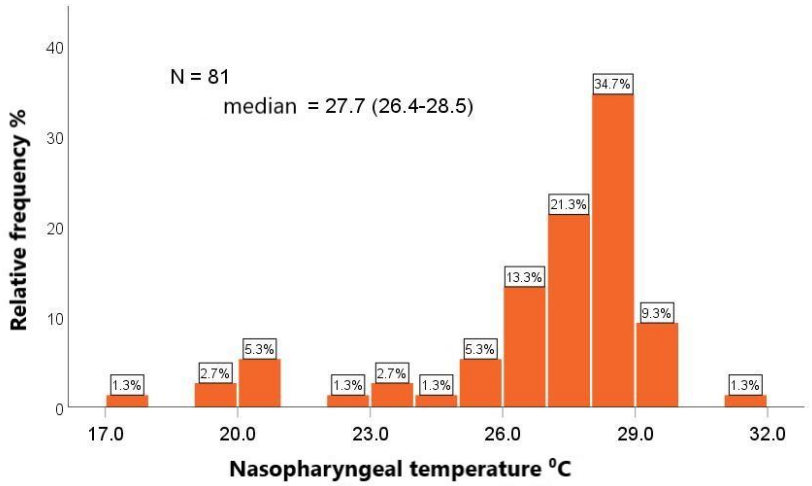

Fig. 13. Histogram of the nasopharyngeal temperature of HCA/ACP in group A.

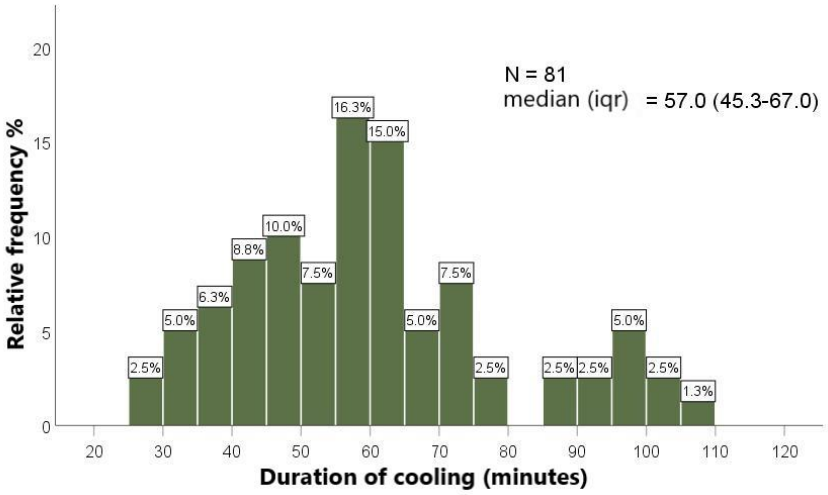

Fig. 14. Histogram of the cooling period in group A.

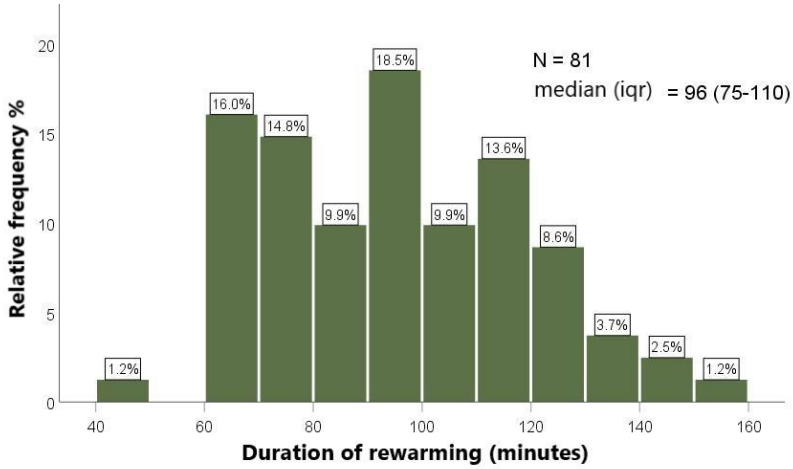

Fig. 15. Histogram of the rewarming period in group A.

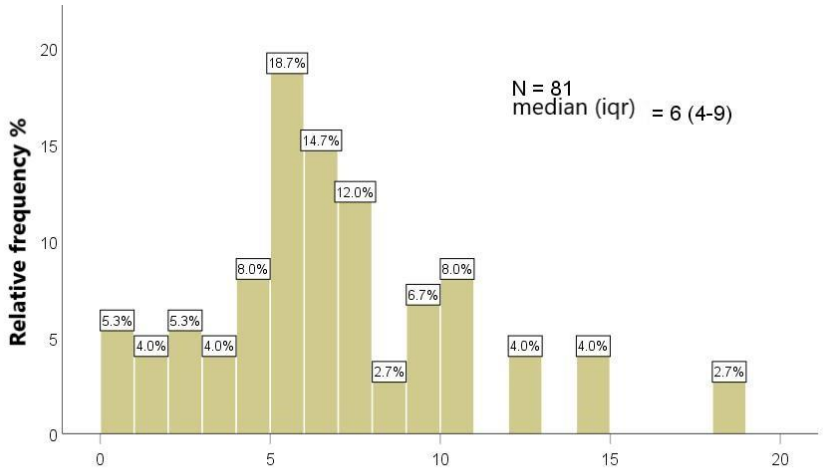

Fig. 16. Histogram of the cold reperfusion period in group A.

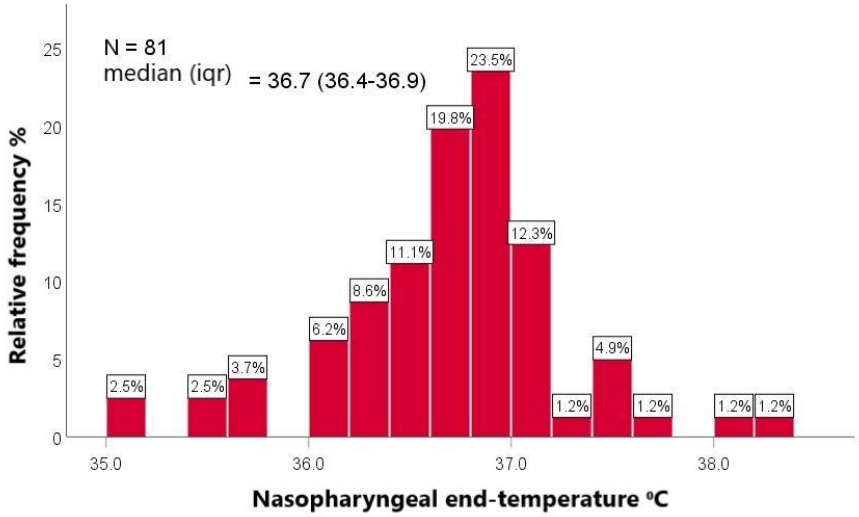

Fig. 17. Histogram of the nasopharyngeal temperature at the end of CPB in group A.

There existed a tendency toward higher corporeal arrest temperatures at later years of the study. The mean nasopharyngeal temperature prior to 2014 was 24.1ºC, whereas beyond 2014 it was 27.8ºC (*p<0.001*) (Fig. 18). The mean rectal temperature prior to 2014 was 27.3ºC, whereas beyond 2014 it was 30.1ºC (*p=0.001*) (Fig. 19).

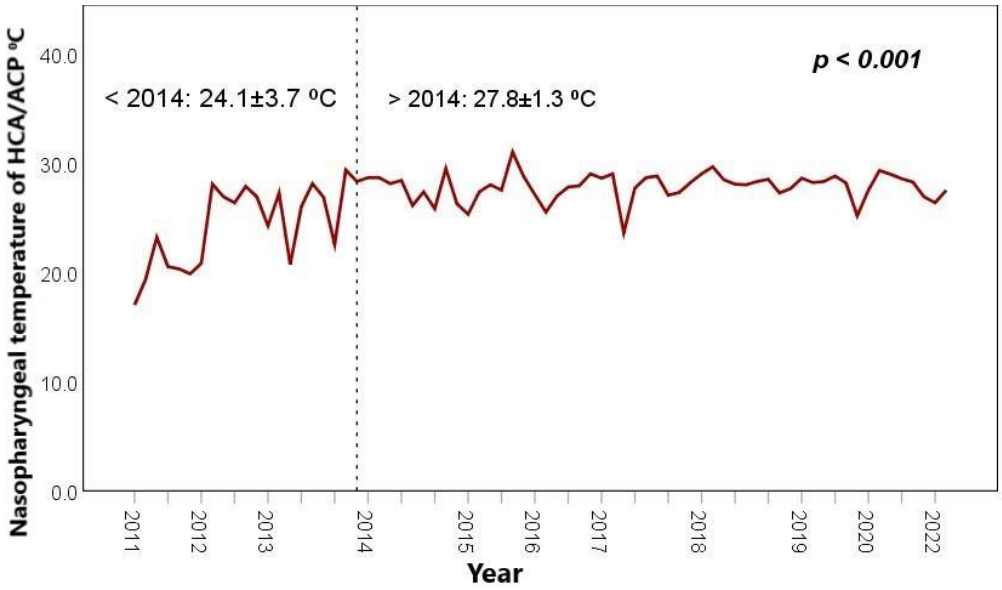

Fig. 18. Line plot illustrating the tendency of nasopharyngeal temperature over the years.

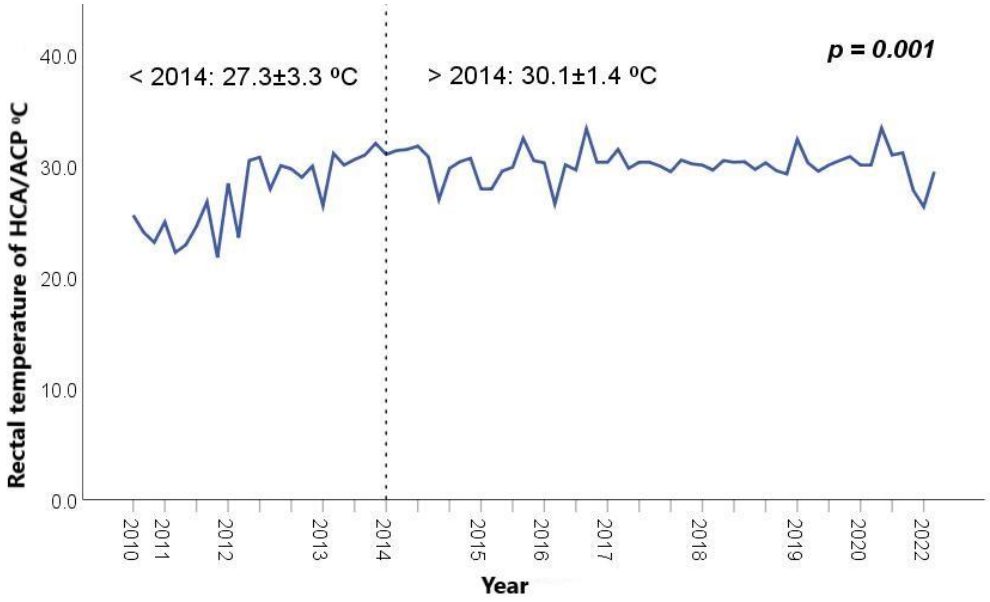

Fig. 19. Line plot illustrating the tendency of rectal temperature over the years.

1.2. Comparison of intraoperative data.

The comparative analysis of intraoperative variables of both groups is shown in table 3.

Intraoperative variable	HCA/ACP n=81	No HCA/ACP n=39	*p*
Operation			
Ascending aorta	55 (67.9%)	20 (51.3%)	
Total arch	12 (14.8%)	0 (0%)	***0.004***
Bentall	10 (12.3%)	14 (35.9%)	
Wheat	4 (4.9%)	5 (12.8%)	
Additional procedure			
Yes	5 (6.1%)	4 (10.3%)	*0.47*
CABG	4 (4.9%)	3 (7.7%)	*1.0*
Mitral valve	1 (1.2%)	1 (2.6%)	
Redo surgery	1 (1.2%)	3 (7.7%)	*0.10*
Pharmacologic protection			
Steroids	63 (77.8%)	34 (87.2%)	
Thiopental	3 (3.7%)	2 (5.1%)	*0.29*
Combination	15 (18.5%)	3 (7.7%)	
Open chest	6 (7.4%)	1 (2.6%)	*0.271*
Reexploration	8 (9.9%)	3 (7.7%)	*0.493*
CPB (minutes)	**161 (137-199)***	138 (107-170)	***0.013***
Cross-clamp (minutes)	103±28	86±39	***0.02***
Perfusion pressure CPB (mmHg)	63±5	65±6	*0.196*
Mean hematocrit (%)	23.8±3.3	24.8±4.4	*0.192*
Lowest hematocrit (%)	20.2±3.6	21.8±5.0	*0.074*
Blood glucose (mmol/L)	12.9±2.7	10.7±3.1	***0.022***
Lactate (mmol/L)	5.1±2.3	2.8±1.5	***0.001***
Nasopharyngeal temperature (ºC)	26.8±2.7	31.4±2.4	***0.000***
Rectal temperature (ºC)	29.2±2.5	32.7±2.7	***0.000***
End temperature (ºC)	36.6±0.6	36.6±0.4	*0.757*

*Table 3. Comparative analysis of intraoperative data between the two groups. *median, parentheses – interquartile range.*

1.3. Summary of the primary postoperative outcome variables.

66 patients (62.9%) had intact neurologic function on awakening, 6 (5.7%) suffered PND (stroke), 22 (21%) – TND, expressed as acute psychosis (delirium) or TIA, 8 patients (7.6%) had late awakening, and 3 (2.9%) remained in permanent coma (Fig. 20). In 15 patients the neurologic status was not described – 8 had died in the operating room or during the first night, and 7 for whom no certain data had been found.

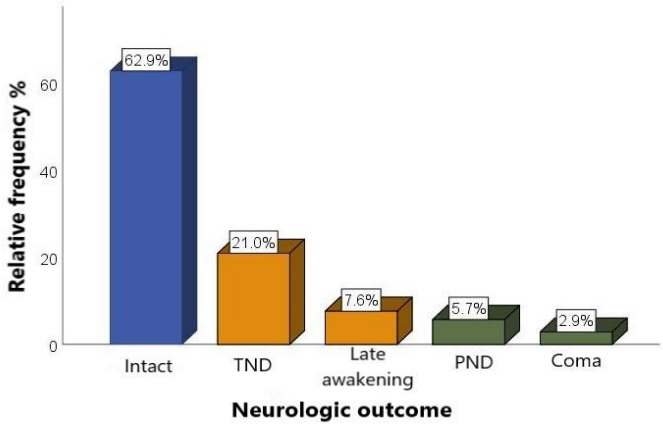

Fig. 20. Bar chart of the distribution of neurologic outcome in all assessed patients (n=105).

Overall mortality was 19 patients (15.8%). 8 patients (6.7%) did not survive the first night (4 died in the operating room and 4 in the intensive care unit). Figure 21 demonstrates the causes of patients' death.

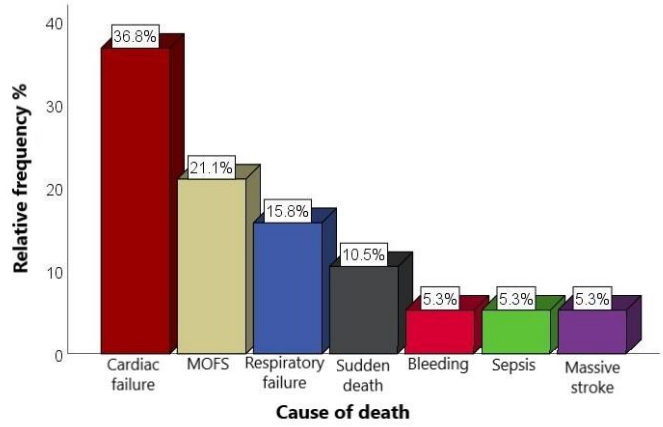

Fig. 21. The bar chart shows the proportion of the various causes of operative death (MOFS – multiorgan failure syndrome).

1.4. Comparison of postoperative results.

Comparative assessment of the secondary and primary outcomes variables is shown in tables 4 and 5, respectively.

Secondary outcome variables	HCA/ACP n=81	No HCA/ACP n=39	*p*
Blood loss			
24 hour	450 (360-810)*	420 (280-1100)	*0.792*
Blood products (total)	10 (7-14)	6.5 (6-10)	***0.004***
Packed red blood cells	5 (4-7)	3 (3-6)	***0.025***
Fresh frozen plasma	5 (3-8)	3 (3-5)	***0.023***
Mechanical ventilation (days)	4 (1.5-7.0)	1 (0.8-5.4)	***0.010***
ICU stay	6.5 (4-11)	5 (3.1-7.4)	***0.038***
Hospital stay	11 (9-17)	11 (9-13)	*0.827*
Lung injury			
Yes	12 (14.8%)	6 (15.4%)	*0.935*
ARDS	9 (11.1)%	2 (5.1)%	*0.266*
TRALI	3 (3.7)%	4 (10.3)%	
Catecholamines			
>24 hours	41 (50.6%)	19 (48.7%)	*0.845*
IABP	8 (9.9%)	2 (5.1%)	*0.496*
Postoperative hemoglobin	100.8±11.3	106.5±13.4	***0.022***
Peak lactate	7.2 (4.4-12.4)	4.7 (3.1-8.1)	***0.021***
Peak creatinine	199 (135-366)	151 (118-223)	***0.036***
Renal replacement therapy	14 (20.9%)	8 (22.2%)	*0.876*
SIRS	5 (7.5%)	3 (8.3%)	*0.875*
Sepsis	6 (9%)	0 (0%)	*0.089*

*Table 4. Comparative analysis of the secondary outcome variables between the two groups. *median, parentheses – interquartile range.*

Primary outcome variables	HCA/ACP n=81	No HCA/ACP n=39	*p*
Neurologic outcome			
intact	41 (59.4%)	25 (69.4%)	
stroke	4(5.8%)	2 (5.6%)	
delirium/TIA	16 (23.2%)	6 (16.7%)	*0.915*
late awakening	6 (8.7%)	2 (5.6%)	
coma	2 (2.9%)	1 (2.8%)	
PND	6 (8.7%)	3 (8.3%)	*1.0*
TND	22 (31.9%)	8 (22.2%)	*0.298*
Operative mortality (overall)	14 (17.3%)	5 (12.8%)	*0.53*
24-hour mortality	7 (8.6%)	1 (2.6%)	*0.158*

Table 5. *Comparative analysis of the secondary outcome variables between the two groups.*

2. Analysis of risk factors for postoperative neurologic injury.

2.1. Comparative analysis between patients with and without postoperative neurologic injury.

The patient suffering postoperative neurologic injury were divided into two clinical categories – permanent neurologic dysfunction (PND) and temporary neurologic dysfunction (TND), and two subcategories – late awakening from anesthesia (a form of TND) and coma (the most severe form of PND).

In order to determine any predictors of adverse neurologic outcome all patients were divided into two groups – patients with intact postoperative neurologic status (n=66) and patients with new-onset neurologic symptoms – PND or TND (n=39).

Key preoperative variable was the neurologic condition at presentation with AAAD. In the following cross-tab the patients were distributed in four groups based on their pre- and postoperative neurologic state (table 6).

Preoperative status	Postoperative result		Total
	Intact	Symptomatic	
Intact	62 (66.7%)*	31 (33.3%)	93 (100%)
Symptomatic	4 (33.3%)	8 (66.7%)	12 (100%)
Total	66 (100%)	39 (100%)	105

*Table 6. Interdependence of the preoperative neurologic status and the postoperative neurologic result. *Percent as a proportion in the subgroup Preoperative status.*

Fischer's exact test for independence of the two variables was significant ($p=0.028$). Therefore the neurologic outcome and the preoperative neurologic status were interdependent. Figure 22 demonstrates that the patients suffering postoperative neurologic injury had significantly more often preoperative neurologic symptoms.

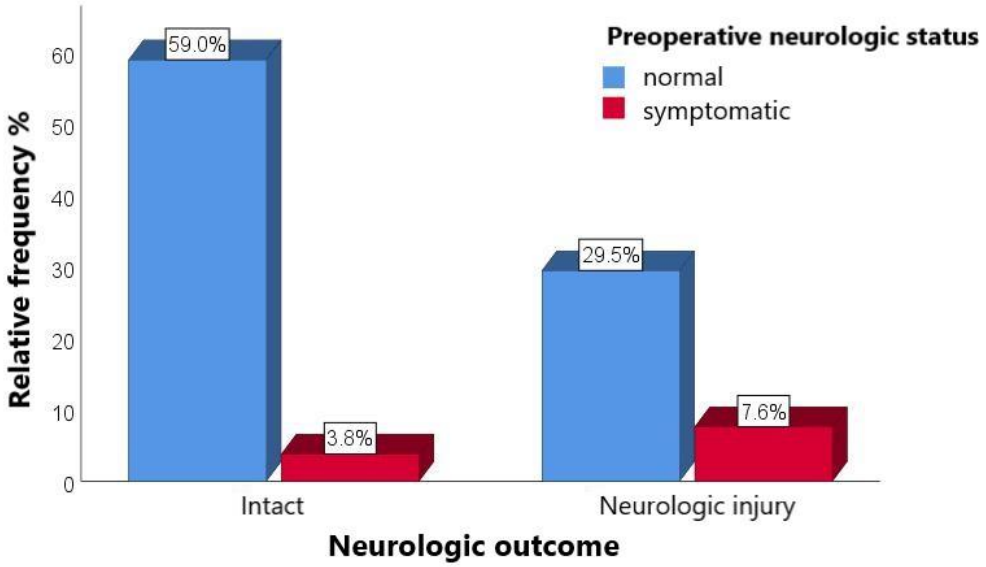

Fig. 22. Bar chart representing neurologic outcome against preoperative neurologic status.

The comparative analysis included preoperative and intraoperative variables since the neurologic result depended on the patient condition before the procedure and the events occurring in the operating room (table 7).

Variable	Intact group (n=66)	Neurologic injury group (n=39)	*p*
Sex (male/female)	74.2%/25.8%	71.8%/28.2%	*0.784*
Age	57.7±12.0	60.5±11.9	*0.252*
Hemoglobin			
Preoperative (g/L)	135.0±17.0	121.7±20.1	***<0.001***
De Bakey type I	47 (71.2%)	32 (82.1%)	*0.214*
Arterial hypertension	61 (92.4%)	36 (92.3%)	*1.0*
Diabetes mellitus	4 (6.1%)	3 (7.7%)	*0.709*
BMI ($kg.m^{-2}$)	28.9±5.9	27.5±4.2	*0.156*
Cerebral vascular disease	1 (1.5%)	4 (10.3%)	***0.062***
Atrial fibrillation	2 (3.0%)	4 (10.3%)	*0.192*
Unstable hemodynamic state	14 (21.2%)	9 (23.1%)	*0.823*
Acute kidney injury	16 (24.2%)	21 (58.3%)	***0.002***
Limb malperfusion	14 (21.2%)	13 (33.3%)	*0.170*
Mesenteric malperfusion	2 (3.0%)	4 (10.3%)	*0.192*
Cardiac tamponade	2 (3.0%)	6 (15.4%)	***0.050***
Operation type*	22 (33.3%)	14 (35.9%)	*0.789*
Steroid + barbiturate	6 (9.1%)	8 (20.5%)	*0.096*
CPB (minutes)	158.5 (127.5-193.3)**	146.5 (125.0-168.5)	*0.424*
Perfusion pressure (mmHg)	64.6±4.7	62.9±4.6	*0.090*
Mean hematocrit on CPB (%)	25.1±3.7	22.7±3.1	***0.001***
Mean blood glucose (mmol/L)	12.5±3.1	11.1±2.2	*0.091*

*Table 7. Comparative analysis of the characteristics of patients with and without postoperative neurologic injury. *Operation differing from isolated ascending aortic replacement; **Median, parentheses – interquartile range.*

2.2. Determination of predictors of postoperative neurologic injury.

The initial regression model included preoperative and intraoperative variables with a probable relation to the postoperative neurologic result.

Upon performing logistic regression with the forward elimination method two independent predictors of neurologic injury were uncovered. They were preoperative *acute kidney injury* (OR: 4.3, 95% CI: 1.7 - 11.0, *p = 0.003*) and the *mean intraoperative hematocrit* (OR: 0.79, 95% CI: 0.69 – 0.91, *p = 0.001*).

Three independent predictors of PND (stroke, coma) were revealed. They were *female sex* (OR: 11.1, 95% CI: 1.4– 87.7, *p = 0.023*), *ischemic heart disease* (OR: 22, 95% CI: 2 – 238, *p = 0.011*), preoperative *mesenteric malperfusion* (OR: 24, 95% CI: 2 – 248, *p = 0.008*). The preoperative acute kidney injury nearly reached statistical significance (*p=0.064*).

One predictor for the development of TND was found – the mean value of *intraoperative hematocrit* (OR: 0.78, 95% CI: 0.66 – 0.91, *p = 0.002*).

3. Analysis of risk factors for operative mortality.

3.1. Comparative analysis between survivals and operative deaths.

The comparative analysis included preoperative, intraoperative, and postoperative variables since the operative mortality depends on patient's condition prior to operation, the intraoperative events, and their recovery in the intensive care unit (Tables 8, 9, and 10).

3.2. Determination of predictors of operative death.

The initial regression model included preoperative, intraoperative, and postoperative variables with a probable relation to operative mortality.

Upon performing logistic regression with the forward elimination method four independent predictors of operative mortality were uncovered. They were the patient's *age* (OR: 1.06, 95% CI: 1.01 – 1.11, *p = 0.015*), *De Bakey type I* dissection (OR: 7.0, 95% CI: 1.3 - 38.0, *p = 0.024*), development of postoperative *lung injury* (OR: 8.5, 95% CI: 1.7 –42.4, *p = 0.009*), and the necessity of *renal replacement therapy* (OR: 13.0, 95% CI: 3.2 – 53.2.0, *p < 0.001*).

After propensity score adjustment it was found that the neurologic outcome (PND and TND) was not an independent predictor of operative death (OR: 0.84, 95% CI: 0.24 – 3.01, *p = 0.789*). The PND itself was not a predictor of operative mortality, too, although the result approaches statistical significance (OR: 3.4, 95% CI: 0.85 – 13.9, *p = 0.083*). The TND was not a risk factor for operative mortality (OR: 1.5, 95% CI: 0.43 – 5.2, *p = 0.535*).

Variables *Preoperative*	Survivals n=101	Deaths n=19	*p*
Gender (Male)	74.3% (75)	63.2% (12)	*0.385*
Age	57.3±12.5	62.3±11.0	***0.026***
De Bakey type I	74.3% (75)	94.7% (18)	***0.013***
Hemoglobin			
Preoperative (g/L)	130.2±17.5	130.0±22.5	*0.971*
Aortopathy	30.7% (31)	10.5% (2)	***0.039***
Arterial hypertension	92.1% (93)	94.7% (18)	*1.0*
Diabetes mellitus	5.9% (6)	15.8% (3)	*0.152*
BMI ($kg.m^{-2}$)	27.6±4.9	29.1±5.8	*0.146*
Ejection fraction (%)	57.8±6.6	57.1±6.4	*0.603*
CVD *Stroke*	5.0% (5)	10.5% (2)	*0.109*
Neurologic symptoms	10.9% (11)	26.3% (5)	***0.040***
Atrial fibrillation	6.9% (7)	10.5% (2)	*0.311*
Ischemic heart disease	5.0% (5)	10.5% (2)	*0.430*
Acute myocardial ischemia	5.0% (5)	15.8% (3)	*0.055*
Unstable hemodynamic state	20.8% (21)	63.2% (12)	***0.001***
Acute kidney injury	29.7% (30)	57.9% (11)	***0.014***
Limb malperfusion	28.7% (29)	31.6% (6)	*0.595*
Mesenteric malperfusion	5.9%% (6)	31.6% (6)	***0.011***
Cardiac tamponade	5.9% (6)	15.8% (3)	*0.152*

Table 8. Comparative analysis of the preoperative characteristics between survivals and deceased patients.

Variables *Intraoperative*	Survivals n=101	Deaths n=19	*p*
Operation type*	37.6% (38)	36.7% (7)	*0.885*
Reoperation	3.0% (3)	5.3% (1)	*0.298*
Open chest/reexploration	14.9% (15)	15.8% (3)	*0.855*
CPB (minutes)	148 (119-169)**	170 (143-205)	***0.002***
Cross-clamp (minutes)	93.9±36.3	103.3±29.8	*0.145*
Perfusion pressure (mmHg)	64.3±4.7	62.9±6.1	*0.170*
Mean hematocrit (%)	24.4±3.7	23.6±3.7	*0.243*
Mean blood sugar (mmol/L)	11.4±2.7	13.5±2.9	***0.010***
Mean lactate (mmol/L)	3.9±2.2	5.3±2.4	***0.037***

*Table 9. Comparative analysis of the intraoperative characteristics between survivals and deceased patients. *Operation differing from isolated ascending aortic replacement; **Median, parentheses – interquartile range.*

Variables *Postoperative*	Survivals n=101	Deaths n=19	*p*
Blood loss *24 hour* (ml)	430 (280-760)*	490 (370-1090)	*0.154*
Blood products *total* (units)	8 (6-10)*	12.5 (8-15.5)	***0.003***
Mechanical ventilation (days)	1.5 (0.8-4)	7.5 (4.4-16.3)	***<0.0001***
Catecholamine	44.6% (45)	89.5% (15)	***<0.0001***
IABP	5.0% (5)	26.3% (5)	***0.013***
Lung injury			
ARDS, TRALI	8.9% (9)	47.4% (9)	***<0.001***
Hemoglobin *mean* (g/L)	105.5±10.5	97.2±13.8	***0.001***
Renal replacement therapy	9.9% (10)	68.4% (13)	***<0.0001***
Sepsis/SIRS	6.9% (7)	36.8%% (7)	***0.001***

*Table 9. Comparative analysis of the postoperative characteristics between survivals and deceased patients. *Median, parentheses – interquartile range.*

4. Influence of HCA/ACP on neurologic morbidity and operative mortality.

4.1. Cross-tabs.

The chi-square test made clear the interdependence of the two variables – the application of HCA/ACP on one side, and the neurologic morbidity or operative mortality, on the other side (tables 11 and 12).

HCA/ACP	Neurologic outcome		Total
	Intact	Symptomatic	
Yes *(group A)*	41 (62.1%)*	28 (71.8%)	69
No *(group B)*	25 (37.9%)	11 (28.2%)	36
Total	66 (100%)	39 (100%)	105

*Table 11. Cross-tabulation examining the distribution of patients from group A and group B according to the postoperative neurologic outcome, p=0.313. *Proportion from the subgroup neurologic outcome.*

HCA/ACP	Operative mortality		Total
	Survivals	Deaths	
Yes *(group A)*	67 (66.3%)*	14 (73.7%)	81
No *(group B)*	34 (33.7%)	5 (26.3%)	39
Total	101 (100%)	19 (100%)	120

*Table 12. Cross-tabulation examining the distribution of patients from group A and group B according to the operative mortality, p=0.530. *Proportion from the subgroup operative mortality.*

4.2. Logistic regression analysis.

Initially a propensity score analysis was performed following the usual methodology. Table 13 show the variables that play a role in the model for calculation of the propensity score.

Preoperative	Intraoperative	Postoperative
Gender	Operation type*	Blood loss *24-hour*
Age	Redo surgery	Blood products (total units)
De Bakey *Type I*	Open chest/reexploration	Mechanical ventilation (days)
Hemoglobin (g/L)	CPB (minutes)	Catecholamines
Diabetes mellitus	Cross-clamp (minutes)	IABP
Arterial hypertension	Perfusion pressure (mmHg)	Lung injury *(ARDS, TRALI)*
BMI ($kg.m^{-2}$)	Mean hematocrit (%)	Mean hemoglobin (%)
Cerebral vascular disease		Renal replacement therapy
Neurologic symptoms		Sepsis/SIRS
Ischemic heart disease		
Acute ischemia		
Unstable hemodynamics		
Acute kidney injury		
Limb malperfusion		
Mesenteric malperfusion		

Table 13. Variables used in the calculation of the propensity score.

After propensity-score adjustment it was found that the utilization of HCA/ACP was not a predictor of *postoperative neurologic injury* (OR = 1.14, 95% CI = 0.33 – 3.9, $p = 0.833$).

After propensity-score adjustment it was found that the utilization of HCA/ACP was not a predictor of *operative mortality* (OR = 1.05, 95% CI = 0.32 – 3.5, $p = 0.936$).

4.3. Comparative analysis of the HCA/ACP parameters with respect to the primary outcome.

A univariate comparative analysis was performed encompassing eight variables which were controlled during HCA/ACP (tables 14 and 15).

Variable	Intact neurologic status (n=41)	Neurologic injury (n=28)	*p*
ACP duration (minutes)	27 (19-33)	26 (21-40)	*0.599*
ACP pressure (mmHg)	71.2±12.6	69.0±11.4	*0.461*
ACP flow (ml/min)	600 (500-800)	625 (500-800)	*0.907*
Nasopharyngeal temperature (ºC)	28.2 (26.2-28.6)	27.9 (26.9-28.7)	*0.430*
Cooling (minutes)	60 (49-81)	55 (39-62)	***0.017***
Rewarming (minutes)	97±23	86±22	***0.046***
Cold reperfusion (minutes)	6 (5-9)	5 (3-8)	*0.109*
End temperature (ºC)	36.7 (36.4-36.9)	36.8 (36.3-37.0)	*0.315*

Table 14. Comparison of ACP parameters between patients with and those without postoperative neurologic injury.

Variable	Survivals n=67	Deaths n=14	*p*
ACP duration (minutes)	27 (20-36)	25 (19-31)	*0.416*
ACP pressure (mmHg)	72.6±12.3	67.0±10.2	***0.029***
ACP flow (ml/min)	600 (500-800)	600 (500-780)	*0.661*
Nasopharyngeal temperature (ºC)	28.0 (25.9-28.5)	27.7 (26.9-28.6)	*0.750*
Cooling (minutes)	54 (43-69)	60 (53-67)	*0.098*
Rewarming (minutes)	90±23	100±23	*0.055*
Cold reperfusion (minutes)	6 (5-9)	5 (2-9)	*0.139*
End temperature (ºC)	36.7 (36.5-36.9)	36.6 (36.3-36.9)	*0.434*

Table 14. Comparison of ACP parameters between survived and deceased patients.

The univariate binary logistic regression found that duration of body cooling significantly influenced the risk of neurologic injury (OR = 0.956, 95% CI = 0.926 – 0.988, *p = 0.007*). If the result was transformed it could be concluded that for every 10-minute shortening of the cooling time the odds of neurologic injury raised 1.6 times. In the same way the duration of body rewarming significantly influenced the risk of neurologic injury (OR = 0.977, 95% CI = 0.957 –

0.996, *p = 0.049*). After the result was transformed, it was shown that for every 10-minute shortening of the rewarming time the odds of neurologic injury raised 1.3 times.

Variables that were significantly different between groups are illustrated by boxplots (figures 23, 24, and 25).

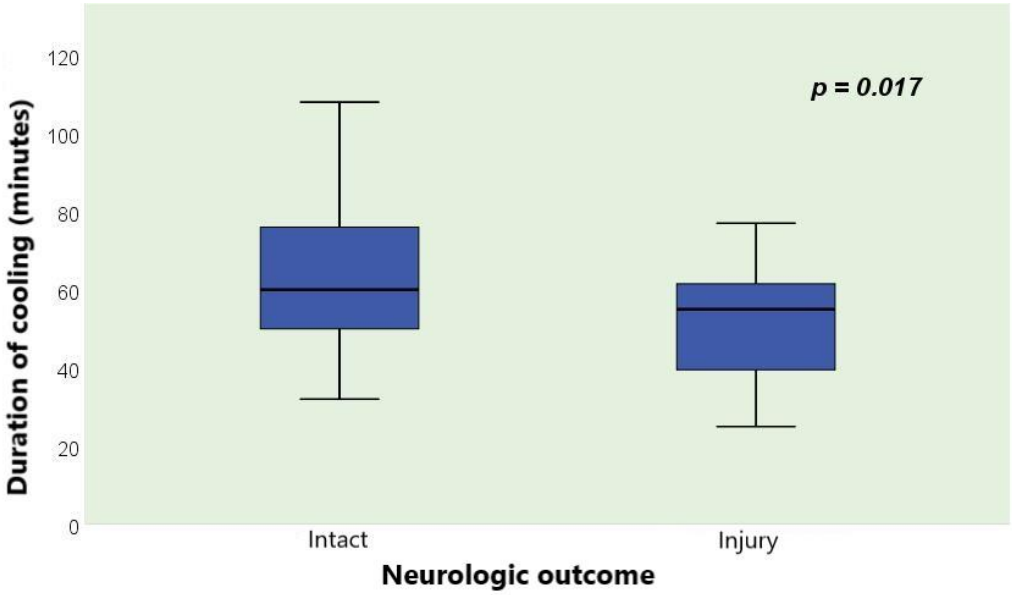

Fig. 23. Comparison of the cooling time between patients with and without postoperative neurologic injury, p=0.017.

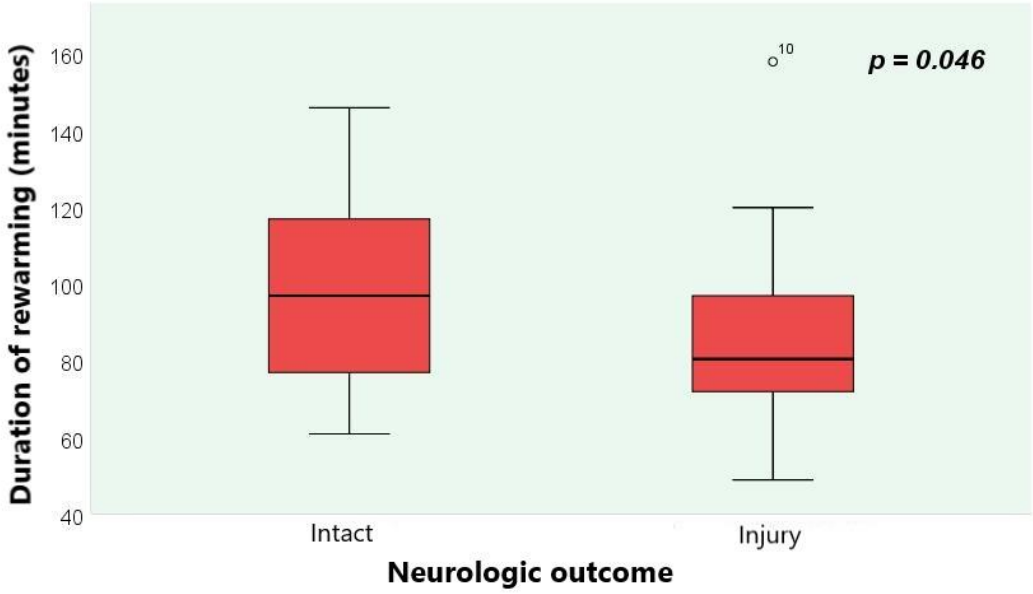

Fig. 24. Comparison of the rewarming time between patients with and without postoperative neurologic injury, p=0.046.

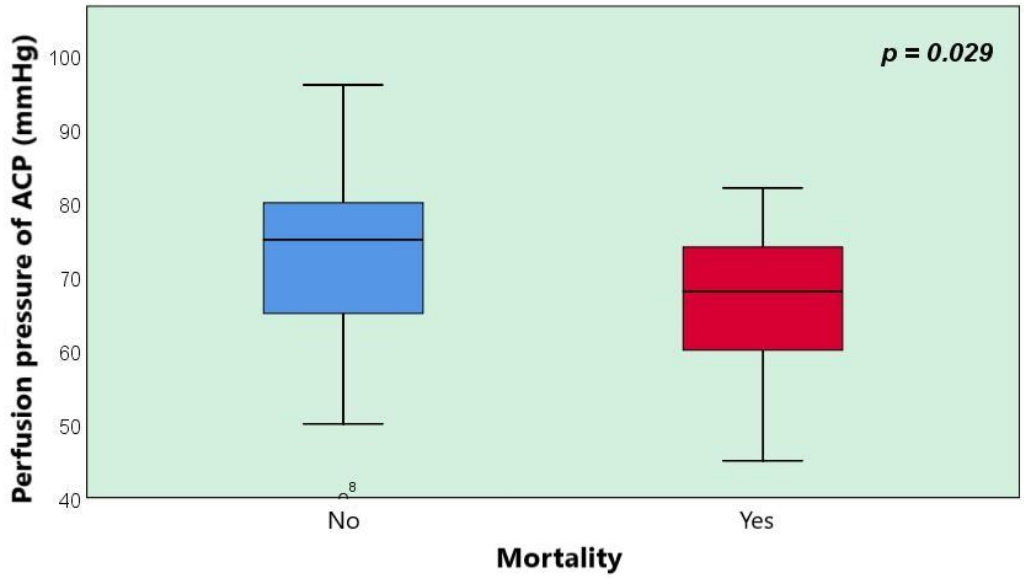

Fig. 25. Comparison of the brain perfusion pressure between survivals and operative deaths, p=0.029.

5. Long-term survival.

5.1. Long-term survival of the whole group.

The mean postoperative survival was 10.5 years (S.E. = 06, 95% CI – 9.4 – 11.7 years). The estimated 5-year survival was 87%, and the 10-year survival was 52% (fig.26).

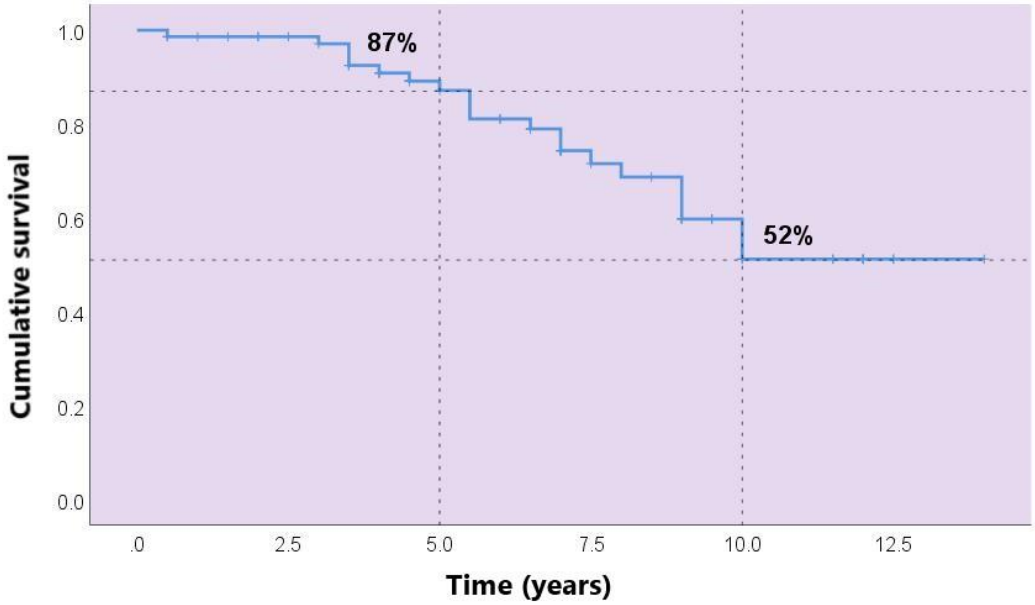

Fig. 26. Survival plot for the whole group.

5.2. Comparative analysis of long-term survival.

5.2.1. HCA/ACP versus no HCA/ACP.

The log rank test (Mantel-Cox) about the difference in survival function was insignificant (*p = 0.396*) with regard to the utilization of HCA/ACP. The mean postoperative survival of group A was 9.5 years (S.E. = 0.6, 95% CI – 8.4–10.6 years). The mean postoperative survival of group B was 11.5 years (S.E. = 1.0, 95% CI – 9.5–13.4 years) (fig. 27).

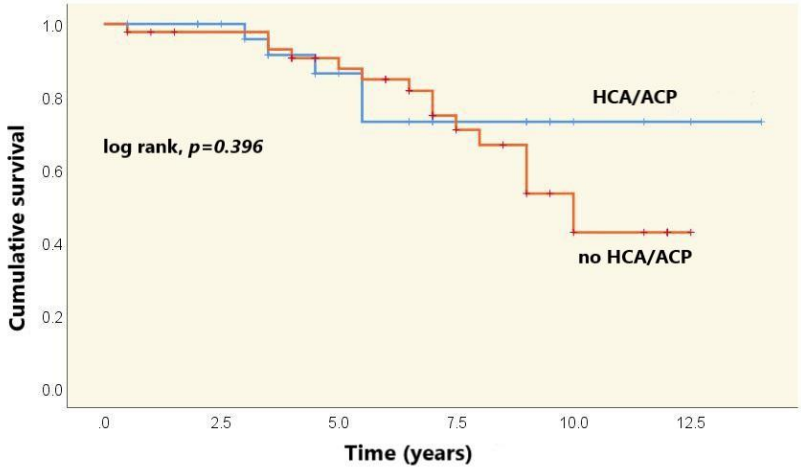

Fig. 27. Survival plots of group A and group B.

5.2.2. According to postoperative neurologic injury.

A log rank test was used to estimate any difference in survival function of patient with and without postoperative neurologic injury, and PND and TND in particular (fig. 28).

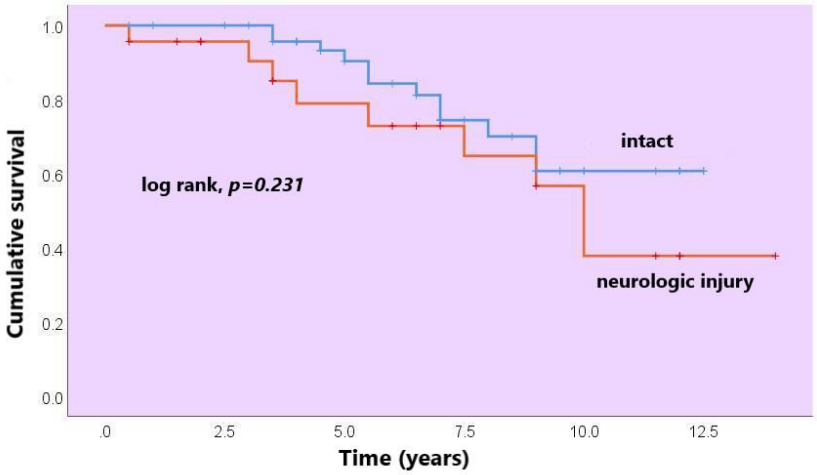

Fig. 28. Cumulative survival of patients with intact postoperative neurologic status and those with neurologic injury (p=0.231).

The curve above shows a tendency toward lower long-term survival of patients with postoperative neurologic injury despite not reaching statistical significance.

The long-term survival of patients with postoperative PND was significantly lower (fig. 29).

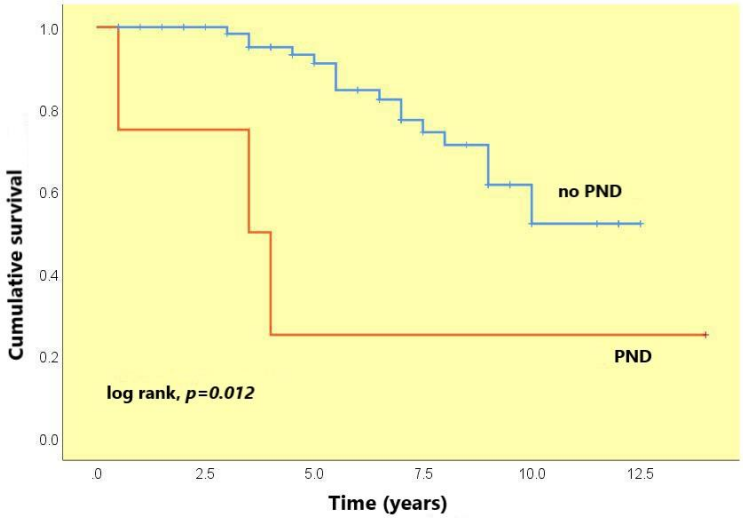

Fig. 29. Cumulative survival of patients with and without postoperative permanent neurologic dysfunction (p=0.012).

No significant difference was found in the survival function of patients with regard to postoperative TND (fig. 30).

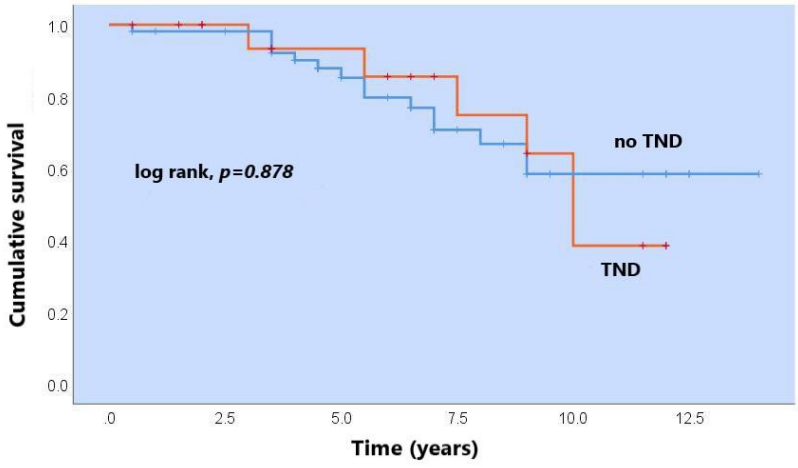

Fig. 29. Cumulative survival of patients with and without postoperative temporary neurologic dysfunction (p=0.878).

5.3. Predictive value of HCA/ACP and postoperative neurologic injury on long-term survival.

After propensity-score adjustment the Cox regression analysis determined that the utilization of HCA/ACP did not predict long-term survival (OR: 1.05, 95% CI: 0.24 – 4.7, *p = 0.949*). The

development of PND had significant negative impact on long-term survival (OR: 4.1, 95% CI: 1.2 – 14.2, $p = 0.026$). The development of TND did not have influence on long-term survival (OR: 1.1, 95% CI: 0.25 – 4.8, $p = 0.897$).

V. DISCUSSION.

The present study investigates the postoperative results of surgical treatment of AAAD with the special point being neurologic morbidity and operative mortality. Two groups of patient were compared – **group A** – open distal anastomosis with HCA/ACP, and **group B** – closed distal anastomosis without HCA/ACP. The hypothermic circulatory arrest is associated with a variety of complications, including neurological, as well as with increased mortality [441], [442], [450], [452]. On the other hand the implementation of antegrade cerebral perfusion allows circulatory arrest under mild-to-moderate hypothermia [423], and improves the postoperative results compared to the isolated HCA [408]. Analyzing any differences between the two groups aimed to prove or reject the safety of HCA/ACP as a method allowing open distal aortic repair.

1. Mean rate of AAAD for the study period.

The mean number of operations for AAAD in the department of cardiac surgery from 2010 to 2022 was 9.2. It was noted the evidently lower number of AAAD cases in the last two years of the study. The reason was probably the effect of the Covid-19 pandemic and its associated redirection of health services. During the first phase of the Covid pandemic there was a 35% decline of the emergency room visits of patients with heart disease and an 18% increase in cardiac mortality [508]. The mean yearly rate of operations for AAAD defines the level of expertise of the relevant cardiothoracic surgery center. Centers with a large volume and expertise carry out at least 11 AAAD surgeries per year, whereas centers with small volume carry out 3 or fewer surgeries [509]. The high-volume centers have lower mortality rate and lower incidence of neurologic complications [44][510]. According to these criteria the department of cardiac surgery in St. Anna University Hospital is a medium- to high-volume center with respect to surgery for AAAD. In this regard the operative mortality of 15.8% and the rate of neurologic complications of 32.5%, in particular the PND rate of 7.5% correlate well with data from recent publications [509], [510].

2. Analysis of demographic and preoperative data.

2.1. Summary and correlation to a referent group.

Variable		Present group	IRAD group
Age		59±12	61.5±14.6
Males		72.5%	67%
Arterial hypertension		92.5%	74.4%
Diabetes mellitus		7.5%	7.7%
Marfan syndrome		3.3%	4.5%
Redo surgery		3.3%	14.2%
Hemodynamic state			
Hypertension		48.3%	36%
Hypotension		20.0%	25%
Shock		6.7%	15%
Pericardial tamponade		7.5%	18%
Renal failure			
Nonoliguric		21.7%	18%
Oliguric		12.5%	
Mesenteric malperfusion		**10%**	**3.7%**
Limb malperfusion		**29.2%**	**9.7% (ischemia)**
Cerebral injury			
Hemiparesis	3.3%		
Stupor	3.3%	9.1%	10%
Delirium	2.5%		
Syncope		4.2%	19%

Table 16. Comparison between preoperative data of the present group and the IRAD group. The assumed differences are shown in bold.

The current research included a successive series of patients origination form a common region – republic of Bulgaria. This ensures consistency in the human material that was used. The demographic characteristics and the clinical presentation were compared to other groups of

patients with AAAD. No significant differences were noted in most parameters (table 16 above) [9].

The present group had more often malperfusion symptoms – renal failure, visceral malperfusion, and limb malperfusion. The cause of this observation was probably due to histological characteristics of the aortic wall in our group leading to a greater extent of aortic disruption with more frequent side branch ischemia.

2.2. Comparative analysis between group A and group B.

The comparative analysis between group A and group B demonstrated insignificant differences in their preoperative characteristics. There was a difference in the mean preoperative hemoglobin (128 versus 135 g/L) which although small was statistically significant (*p=0.049*). In group A patients with type I dissection prevailed whereas in group B type II dissection was more frequent. This determined the surgical behavior as type I dissection often mandates open distal repair with HCA/ACP. Group B contained more patients with nonsyndromic aortopathy and Marfan syndrome. In group A there was a greater proportion of acute kidney injury stemming from the abdominal involvement in type I dissection. The remaining characteristics were nearly equal.

3. Analysis of intraoperative data.

3.1. Summary and correlation to a referent group.

The intraoperative data of the present group was compared to a group of patients operated for AAAD from July 2011 to September 2012 and included in the STS Registry (Society of Thoracic Surgeons) (Table 17)[44].

Variable	Present group	STS group
Procedure		
Aortic replacement + commissural resuspension	73.3%	54%
David/Yacoub	0%	2.3%/0.3%
Bentall-de Bono	19.2%	24.6%
Wheat	7.5%	13.1%
CABG	5.8%	14.3%
Mitral valve repair/replacement	1.7%	1.4%
Arterial cannulation		
Ascending aorta	**98.3%**	**29.1%**
Femoral artery	**1.7%**	**45.9%**
Subclavian/axillary artery	**0%**	**31.0%**
CPB		
Perfusion time	161±50	195±80
Cross-clamp	96±33	113±58
Lowest T°C of HCA	**29.2±2.7**	**21.4±5.4**
Lowest hematocrit	**20.7±4.2**	**23.0±4.8**
HCA		
No HCA	32.5%	21.3%
HCA without cerebral perfusion	**0%**	**31.3%**
ACP	**67.5%**	**23.8%**
RCP	**0%**	**19.7%**
ACP + RCP	0%	3.0%
ACP duration (minutes)	28±13 (median 26, iqr 19.0-33.0)	34±21

Table 17. Comparison of intraoperative data between the current group and the STS group. The assumed differences are shown in bold.

The duration of CPB and cross-clamp were comparable with the data published for the STS group. The CPB perfusion pressure (64±5 mmHg) and the level of maintained hematocrit (24.1±3.7

percent) correspond to the most recent recommendations for CPB [511]. The mean lowest rectal temperature was 30.6±2.6ºC which fell into the category of mild-to moderate hypothermia according to the accepted consensus statement [335]. The hyperglycemia (mean blood glucose values of 12.3±3.0 mmol/L), which was observed, was due to peripheral insulin resistance – a common sequel of hypothermia and surgical stress, and is typically difficult to control even on high-dose insulin therapy [512]. The operative mortality increases threefold at peak values of blood glucose above 20 mmol/L [512]. In our group we found 14 patients with peak plasma glucose during CPB above 20 mmol/L and their mortality rate was extremely high – 71.4% or more than four times the average mortality. Apart from its proven effects on neutrophil function, endothelium, and blood-brain barrier, the hyperglycemia could be a surrogate marker of the severity of surgical stress, which is itself related to elevated mortality [512]. The intraoperative hyperglycemia worsens the postoperative neurocognitive outcome even in nondiabetics [513].

The duration ACP correlated well with published data about other large groups of patients with AAAD (28±13 min versus 34±21 min for STS). The duration of ACP in the present group was actually the same as the duration of HCA – median 26 versus 27 minutes. The small difference was accounted for by the less than a minute period of total circulatory arrest required for cannulation of the brachiocephalic arteries and initiation of bilateral cerebral perfusion. Despite hypothermia and the consequent suppressed cerebral metabolic rate the ACP perfusion pressure was maintained at physiologic ranges of 70±12 mmHg. These values corresponded well to the upper margin of the accepted recommendations [160], [420]. In most cases this perfusion pressure was achieved with a perfusate flow of 8-10 ml/kg/min. Thus the median perfusion flow of ACP in group A was 600 ml/min. Perfusion flows of 8-10 ml/kg/min are optimal as higher value raise the intracranial pressure and impair neurologic outcomes [200], [401].

The cold reperfusion following HCA/ACP is mandatory. It allows the body to be reperfused at a temperature equal to the arrest temperature. This approach reduces the early oxidative stress, helps clear toxic metabolites, reduces the intracranial pressure, and enhances brain blood flow [338]. A 10-minute cold reperfusion improves neurologic results following HCA with or without cerebral perfusion [339]. The median duration of cold reperfusion was 6 minutes (iqr from 4 to 9), which corresponds well to the proven interval of 5 to 10 minutes.

The duration of cooling was longer as the target temperature was lower (r = -0.225, *p = 0.016*). The objection of higher arrest temperature shortens the period of corporeal cooling and thus the duration of CPB. The nasopharyngeal temperature correlated tightly to the rectal temperature during cooling (r = 0.877, *p = 0.000*). This proves that the central cannulation method for AAAD surgery achieves efficient cerebral as well as corporeal cooling without significant risk of malperfusion. The duration of rewarming (90.8±24.2 minutes) was higher than the duration of cooling (55.8±20.6 minutes), the difference being 35.0±2.4 minutes (*p<0.*0001). This was due to the lower temperature gradient between perfusate and body (up to 6ºC) at rewarming compared to the gradient at cooling (up to 10ºC). The low rewarming temperature gradient prevents formation of gaseous microbubbles in interstitial and intracellular space [221]. A recent experimental study by Linardi et al confirmed the favorable effect of slow rewarming after HCA (90 minutes for HCA at 19ºC). The slower cooling reduced the brain inflammatory response, oxidative stress, and apoptosis, increases brain blood flow, and reduces brain edema [514].

3.2. Comparative analysis of intraoperative results between group A and group B.

The distribution of operation types showed significant difference between groups (*p = 0.004*). Total arch replacement was only performed in group A under HCA/ACP – 14.8% versus 0%. Aortic valve replacement (isolated or as a composite graft) was performed more often in group B. A probable reason was the expected prolongation of operation which forces the surgeon to avoid the additional stress of HCA and perform a closed distal repair. The surgical and physiological stress was more pronounced in group A than group B. The CPB duration was longer in group A (161 versus 138 minutes, *p=0.013*). The most probable cause was the lower target temperature in group A, necessitating longer cooling and rewarming. The difference in cross-clamp times although statistically significant was not great as an absolute value (103 versus 86 minutes, *p=0.02*). This difference was due to the often more complex surgical correction of the aorta in HCA cases, sometimes involving whole arch replacement. The nasopharyngeal and rectal temperatures differ significantly between groups (*p < 0.001*). This was natural as the lower body temperature provided ischemic protection under circulatory arrest. In group A the plasma glucose values were on average higher (12.9 versus 10.7 mmol/L, *p = 0.022*) which was inherent to the hypothermia and its associated insulin resistance [515]. Despite the hypothermia cellular metabolism continues at low rates even during circulatory arrest and lactate accumulates in tissues.

This was why the mean intraoperative lactate in group A was greater than in group B (5.1 versus 2.8 mmol/L, *p=0.001*). The nadir hematocrit value in group A was lower, as the difference was close to statistical significance (20.2% versus 21.8%, *p=0.074*). As blood temperature drops its viscosity increases which can be corrected by hemodilution [189]. However, some studies showed that significant hemodilution led to insufficient tissue oxygenation and worse neurologic result [191], [192]. The rest of variables did not differ significantly between groups.

4. Analysis of postoperative results.

4.1. Summary of postoperative results and correlation to a referent group.

Table 18 presents correlation of our results to those of another group. Comparing the study group with patient from the STS registry, no evident differences were found with regard to postoperative parameters, and more specifically neurologic injury and operative mortality.

Variable	Present group	STS group
Blood products		
Packed RBCs/FFP	5/4	5/4
Reexploration for bleeding	9.2% (11)	8.7%
Prolonged mechanical ventilation (>72 hours)	45% (50)	53%
ICU stay (days)	6	4.7
Hospital stay (days)	11	9
Sepsis	5% (6)	4%
SIRS	6.7% (8)	-
Renal replacement therapy	**19.2% (23)**	**8.4%**
Neurologic injury *PND + coma*	8.6% (9)	12.8%
Operative mortality	15.8% (19)	17.4%

Table 17. Comparison of postoperative data between the current group and the STS group. The assumed differences are shown in bold.

4.2. Comparative analysis of postoperative results between group A and group B.

Group A and group B were compared by several basic postoperative parameters which uncovered some important disparities. Although postoperative blood loss in the first day did not differ (450 ml against 420 ml, respectively, *p=0.792*), patients from group A were transfused more units of blood products – packed RBCs/FFP: 5/5 against 3/3, *p=0.004*. Considering the higher preoperative hemoglobin in group A, the difference in blood product utilization was probably due to a greater intraoperative blood loss (not recorded in the current study). Lower operative temperatures with HCA/ACP worsened patients' hemostatic reaction. Also, HCA/ACP with open distal repair was used in cases of more severe intimal tears and fragile aortic wall, which are risk factors for anastomotic bleeding. The equality in postoperative blood loss showed that despite the application of HCA/ACP a definite hemostasis was achieved at the end. Nevertheless the postoperative hemoglobin in group A was lower (100.8 against 106.5 g/L, *p=0.022*).

Another parameter that differed between groups was the duration of mechanical ventilation in the intensive care unit. It was longer in group A (a median of 4 days versus 1, *p=0.01*). In an experimental model Cooper et al proved that HCA caused endothelial dysfunction in tissues, most pronounced in kidneys and lungs [442]. The microvascular dysfunction causes water retention which impairs pulmonary gas exchange and demands more prolonged mechanical ventilation. In group A peak creatinine values were higher (199 versus 151 μmol/L, *p=0.032*). This was due to the endothelial dysfunction and kidney injury, caused by HCA [442]. Resolution of homeostatic derangements in group A required longer stay in the intensive care unit (median of 6.5 versus 5 days, *p=0.038*). Peak lactate in group A was higher (7.2 versus 4.7 mmol/L, *p=0.021*). The anaerobic glycolysis during circulatory arrest led to accumulation of lactate in cells and tissues. Also, the CPB is associated with regional malperfusion in some tissues due to metabolic dysregulation or microembolism as well as tissue edema which further impairs cellular gas exchange and tissue oxygenation [443]. The duration of CPB in group A was higher which thus contributed to higher lactate. The operative mortality and the rate of neurologic complications did not differ between the two studied groups. Malvindi et al did not find difference in these primary outcome parameters in similar groups [506].

5. Assessment of risk factors for adverse outcome.

5.1. Risk factors for postoperative neurologic injury.

Nearly two thirds of patients had uneventful neurologic recovery after the operation. The proportion of patients with PND (stroke and coma) was acceptable (8.6%) and comparable to results of other authors. Acute psychosis (delirium) and late awakening from anesthesia were noted in 30% of patients, which was considerable, but corresponds to the disease nature and burden of the operation.

Patients with preoperative neurologic deficit more often develop new postoperative neurologic symptoms [518], [519]. Such association was also evident in our group ($p=0.028$). This was not unexpected bearing in mind that all neurologic symptoms in AAAD arise from cerebral hypoperfusion which is sometimes as severe and prolonged to cause residual symptoms after the operation. The chart of distribution of neurologic outcome with respect to preoperative neurologic symptoms clearly illustrates the difference (fig. 22).

The univariate analysis compared certain characteristics of patients with and without postoperative neurologic injury. It provided a clue to key differences. The two groups had statistically significant differences in four parameters – preoperative hemoglobin, acute kidney injury, cardiac tamponade, and the intraoperative hematocrit values. Patients with postoperative neurologic injury had higher prevalence of previous stroke as the difference nearly reaches statistical significance. Patients with postoperative neurologic injury had lower hemoglobin on presentation, more often presented with preoperative acute kidney injury and cardiac tamponade, and lower intraoperative hematocrit.

Logistic regression analysis was used to reveal those factors that independently predicted the probability of postoperative neurologic injury. These were the preoperative acute kidney injury and intraoperative hematocrit. The acute kidney injury could be assumed to harm the brain through accumulation of toxic metabolites or it predicted greater aortic wall trauma with greater risk of organ and brain malperfusion. The level of hemoglobin evidently had an important role in cerebral oxygenation in the setting of compromised hemodynamics. The intraoperative hematocrit is a modifiable risk factor which has to be strictly monitored and maintained within appropriate range for better results.

Risk factors for PND were female gender, ischemic heart disease, and mesenteric malperfusion. The acute kidney injury almost reached statistical significance. Risk factor for TND was the intraoperative hematocrit. Exclusive of the hematocrit all other factors were non-modifiable and mainly affected our prognosis of patients.

5.2. Risk factors for operative mortality.

The known predictors of operative mortality allow making a prognosis for a given patient and an opportunity to intervene to lower mortality. Key risk factors for operative mortality in AAAD surgery were stated to be preoperative neurologic injury [43], [72], organ malperfusion, mesenteric malperfusion in particular [62], [74], acute kidney injury, preoperative cardiac tamponade and shock, as well as advanced age [44].

The operative mortality in the present group was 15.8%, which correlates to the average mortality of this type of operations with the current advances of cardiac surgery. More than a third of patients died of cardiac failure. Cardiac failure was the most common mode of intraoperative death. The prolonged cross-clamp times, any preoperative myocardial ischemia or acute aortic regurgitation with myocardial distention were all factors for development of heart failure. One fifth of all patients died of multiorgan failure, which evolved slowly over the course of treatment in the intensive care unit, despite resolution of proper hemodynamics. Next in significance was severe lung injury with intractable hypoxemia. Two patients died suddenly after uneventful recovery and the suspected cause was acute massive aortic hemorrhage. According to literature the main causes of early death were acute cardiac failure, bleeding, cerebral injury, and various malperfusion syndromes [520].

The univariate analysis showed significant difference in a large number of parameters between survivals and deceased patients. Patients who died were older (62 versus 57 years), more often with type I dissection and less often with aortopathy. Also, deceased patients had higher incidence of preoperative neurologic symptoms, unstable hemodynamics, acute kidney injury, and mesenteric malperfusion. Longer duration of CPB, higher intraoperative blood glucose and lactate were more frequent findings in fatal cases. The differences in various parameters of postoperative intensive care were also substantial. Patients who subsequently died were transfused more units of blood products, had lower postoperative hemoglobin, longer mechanical ventilation, greater need for vasopressor or inotropic support and IABP, more often develop acute lung injury, sepsis/SIRS,

and had a higher need for renal replacement therapy. Some of these factors physiologically interact between each other. Thus multivariable logistic regression was performed to account for such interactions. Four independent predictors of operative mortality were uncovered in the present group. Age was a common risk factor known in many other studies. The postoperative lung injury raised the chance of death due to refractory hypoxemia and end-organ damage. Patients requiring renal replacement therapy had more severe kidney injury with consequent secondary complications and death. Type I aortic dissection was also an independent risk factor for death. This may have been due to the significantly elevated risk of organ malperfusion in type I dissection. Some studies also pointed the postoperative neurologic injury as a risk factor for mortality [36]. In our study PND nearly reached statistical significance as a predictor of death (*p=0.083*), whereas TND was not a predictor.

6. The application of antegrade cerebral perfusion – effect on neurologic morbidity and operative mortality.

6.1. With or without HCA/ACP?

There is currently a consensus statement that the open distal anastomosis during ascending aortic replacement is to be first choice [507]. The open distal anastomosis is only performed when methods of cerebral protection are employed [506]. The antegrade cerebral perfusion with mild-to-moderate hypothermic circulatory arrest is an effective method for cerebral protection with low rates of neurologic complications and operative mortality [61], [157]. The present study compared two patient groups with AAAD. Group A included patients operated under mild-to-moderate HCA with complementary ACP (open anastomosis). Group B included patients operated under mild systemic hypothermia without HCA/ACP (closed anastomosis). Comparing the two groups allowed assessment of the effect of HCA/ACP on postoperative neurologic morbidity and operative mortality.

Propensity score analysis was used to take into account all potential disparities between groups A and B I with regard to clinical parameters that would have altered the proper assessment. After logistic regression with propensity score adjustment it was concluded that HCA/ACP *was not a predictor* of either postoperative neurologic morbidity or operative mortality.

6.2. Effect of HCA/ACP parameters on primary outcome.

The method of HCA/ACP should be performed under certain perfusion conditions. The proper control of parameters through the heart-lung machine is able to exert influence on the neurologic outcome and operative mortality. In the current group the HCA/ACP parameters were maintained within ranges than have proved to generate the best results based on evidence from the last 30 years.

The implementation of ACP significantly prolongs the safe interval of HCA. The duration of HCA/ACP in the current group was acceptable and comparable to other groups [422]. It was much lower than values reported to have been associated with elevated neurologic risk [61]. Therefore the adverse outcome which afflicted some patients was not due to HCA/ACP duration. The perfusion pressure did not differ between patient with and without neurologic injury. This could be attributed to the constant range of 60-80 mmHg, which is recommended [401]. Deceased patients had lower perfusion pressure than survivals (72.6 against 67.0 mmHg, $p=0.029$) although the absolute difference was not large. Here unaccounted factors may have influenced the mortality. There was no difference in perfusion flow between patient with favorable and unfavorable neurologic outcome. ACP perfusion flow was controlled within the tight range of 6-10 ml/kg/min which is recommended. In brain perfusion the required flow was calculated on the ideal body weight since the brain mass does not increase with body weight. Also, the difference in perfusion flow in men and women is less than 10% [522]. With age the total brain mass decreases although this is not an argument to correlate flow to age [522]. ACP was carried out at nasopharyngeal temperature of about 28ºC in most patients. This temperature was accepted as optimal and associated with good postoperative results [61], [440]. That is why temperature was not a factor that have affected results in the current group. Although cooling and rewarming after HCA were performed under a certain temperature gradient between perfusate and body, each patient took different time to reach the desired temperature. The duration of cooling is said to be no less than 30 minutes [337]. The slow cooling restricts formation of gas emboli in the blood and improves neurologic results [221]. Slow rewarming is also preferred over fast rewarming. Linardi's experimental model shows that the slow rewarming (90 minutes versus 45 minutes fast rewarming) starting from 19ºC is correlated with lower activation of cytokines in the brain, better brain blood flow and edema reduction in the brain parenchyma. According to current guidelines patient

rewarming should be occurring at a speed of 0.25-0.5ºC/min [221]. In the present group rewarming started at about 28ºC as its duration was a little more than 90 minutes which can be nested under the heading "slow rewarming". Going back to comparative analysis it can be seen that patients with postoperative neurologic injury had significantly shorter durations of cooling and rewarming. Regression analysis showed that 10-minute shortening of cooling increased the risk of neurologic injury 1.6 times, whereas 10-minute shortening of rewarming increased this risk 1.3 times. The strategy of using a maximal temperature gradient of 10ºC in cooling and 6ºC in rewarming was successful and recommended considering the favorable neurologic results. It must be noted that the maximal perfusate temperature in rewarming was 37ºC [221]. Therefore with progression of rewarming the gradient between body and perfusate narrowed and thus the speed of rewarming. This on itself prolongs the CPB. However, two benefits existed – thermal injury of blood components and the risk of brain hyperthermia were avoided. A 10-minute cold reperfusion of the body following HCA with or without cerebral perfusion improves neurologic results [339]. In our group the duration of cold reperfusion after HCA/ACP was 5-6 minutes and there was no difference between patients with or without neurologic injury. Thus we concluded that 5 to 10-minute cold reperfusion was enough to improve the neurologic result. The end nasopharyngeal temperature was maintained within narrow borders a bit higher than 36.5ºC, but not higher than 37.0ºC to prevent cerebral hyperthermia. That is why no difference existed in end temperature between patient with uneventful neurologic recovery and those with neurologic injury.

7. Long-term survival after AAAD surgery.

The patient who had undergone surgery for AAAD was expected to live on average of 10.5 years afterwards. Taken from another perspective. 5-year survival was 87%, which corresponded well to data from other authors [76], [77]. 10-year survival was 52% and it was lower than the 70%-and-above survival reported in other studies [77]. The reasons for the sharp decline in survival in our group were difficult to clarify. The absence of an established national policy for follow-up and secondary prophylaxis after AAAD surgery may be one such reason. Late follow-up after AAAD surgery should consist of CT-aortography, echocardiography, as well as assessment of cardiovascular risk factors. Unknown aneurysmal dilatation of the remaining aorta, development of heart failure, and poorly controlled arterial hypertension all contribute to late mortality. In our group the expected duration of life after operation was 11.4 years for males and 7.4 years for

females. Considering that the mean age of males was 56.3 years and 67.0 years for females it can be estimated that the average life expectancy was about 68 years in males and 74 years in females. According to data from the National Statistical Institute the average life expectancy for the period 2010-2020 was relatively stable and equals 71.1 years for males and 78.2 years for females. Therefore in the present group the duration of life was 3 years less in males and 4 years less in females than that expected for the general population.

Comparative analysis of the survival function of group A (open anastomosis with HCA/ACP) and group B (closed anastomosis without HCA/ACP) did not show significant difference (*p=0.396*). Other studies did not find a difference between similar patient groups either [505], [506], [523]. Some studies even demonstrated better long-term survival with HCA/ACP [524]. Olsson et al. stated that the open distal anastomosis was an independent predictor of reducing long-term mortality [76]. Nguyen et al followed up two groups – with open and closed distal anastomosis. Five years onward the closed group had more often false lumen perfusion and residual flap in the aortic arch [525]. Persistent false lumen can be responsible for progressive dilatation of the thoracic aorta and is an independent risk factor for late death [526]. The method of open distal repair with HCA/ACP allows more extensive resection of the dissected aorta including the zone of manipulation (central cannulation and cross-clamp site). This along with the greater precision of the anastomosis raises the rate of false lumen thrombosis.

Long-term survival of patients with postoperative neurologic injury did not differ from survival of patients with intact neurologic recovery (*p=0.231*). Most patients in the neurologic injury group had TND, which was reversible, and apart from prolonging hospital stay, did not affect long-term survival. If the PND subgroup was reviewed separately, it became evident that postoperative long-term survival of PND patients was significantly lower (*p=0.012*). Patients with postoperative stroke needed extended rehabilitation, suffer immobilization with a risk for infectious complications, loss of social contacts, and occupation. These factors may cause their earlier demise.

In order to account for the influence of other patient factors on long-term survival propensity-score adjustment was performed along with Cox-regression. The application of HCA/ACP was not an independent predictor of long-term survival, i.e. it had neither positive nor negative effect (*p=0.949*). Variations in patient survival depended on other factors. Postoperative PND was an

independent predictor of postoperative survival as it increased the risk of late death 4.1 times on average (*p=0.026*). PND was confirmed by other studies to raise the risk of late death [77]. TND was not an independent risk factor for late death.

VI. DEDUCTIONS.

1. The mean yearly number of operations for AAAD in the heart surgery center from which the current patients were recruited was 9.2 for the period 2010-2022 and it corresponds to medium-to-high volume of surgery for this disease. Therefore the interpretation of results may be assumed to be reliable about the Bulgarian population.

2. The patient sample was similar to other groups from large international databases with respect to demographic and clinical parameters but the current groups presented more often with acute renal failure and organ malperfusion.

3. The two formed groups (group A and B) were almost equal in terms of demographic and clinical characteristics which contributed to reliability of results. Group A was noted to have more often some characteristics linked to higher risk.

4. The operative strategy in our group differed in some ways from the approach accepted by large international cardiovascular surgical centers. Principal differences were arterial cannulation through the dissected ascending aorta in all patients, mandatory addition of ACP to HCA, non-use of retrograde cerebral perfusion, and maintenance of higher corporeal temperature during circulatory arrest.

5. The conduct of CPB and HCA/ACP was performed along established guidelines.

6. In group A the duration of CPB and myocardial ischemia were higher which was due to more complex surgical corrections and longer duration of cooling/rewarming.

7. The postoperative results of the main clinical parameters did not differ from those of large international databases.

8. Some notable differences in important clinical parameters in favor of group B were observed. However, the implementation of HCA/ACP in group A did not increase the risk of adverse outcome – neurologic injury and operative mortality.

9. Independent risk factors for postoperative neurologic injury were the preoperative *acute renal injury* and the low *intraoperative hematocrit.* Risk factors for permanent neurologic dysfunction were *female gender, mesenteric malperfusion,* and *ischemic heart disease.*

10. Independent risk factors for operative mortality were *advanced age, type I dissection, postoperative lung injury,* and the need for *renal replacement therapy.* PND did not turn out to be an independent predictor although the result was close to statistical significance (*p=0.083*).

11. Fast cooling and rewarming worsened the neurologic results. The temperature gradient during cooling was not higher than 10 degrees, and during rewarming – not higher than 6 degrees.

12. The application of HCA/ACP along the established protocol in the cardiac surgery center in St. Anna Hospital, Sofia, *was not a risk factor* for postoperative neurologic injury, PND in particular, and operative mortality.

13. The long-term survival in the present group was comparable to most reports on this topic, despite the evident decline after 5 years.

14. The application of HCA/ACP was not a risk factor for late death. The development of postoperative PND worsened the long-term survival.

VII. CONCLUSION.

The acute type A aortic dissection is a life-threatening disease which requires emergent surgical intervention. The operative procedure often necessitates a radical approach with the application of hypothermic circulatory arrest and cerebral perfusion. The method of mild or moderate hypothermic circulatory arrest and bilateral selective antegrade cerebral perfusion ensures very good results with regard to neurologic recovery, operative mortality, and long-term survival. Therefore this method is recommended for the performance of open distal anastomosis in all patients with acute type A aortic dissection.

VIII. CONTRIBUTIONS.

1. As far as the author is informed, this is the first study investigating the topic of cerebral protection during AAAD surgery in the Bulgarian population.

2. In particular, the application of selective antegrade cerebral perfusion in the setting of mild-to-moderate hypothermic circulatory arrest was analyzed. The optimal perfusion conditions were described, which lead to best postoperative results according to our data and published literature.

3. The independent predictors of adverse outcome were analyzed – postoperative neurologic injury, in particular permanent and temporary neurologic dysfunction, and operative (30-day) mortality.

4. The effect of the aforementioned approach of cerebral protection on adverse outcome – neurologic injury and death, was analyzed.

5. The long-term survival following operation for AAAD was estimated.

6. The effect of the aforementioned approach of cerebral protection on long-term survival was analyzed.

7. The good and even better results achieved with HCA/ACP compared to older methods, which are nevertheless still widespread in clinical routine, were confirmed.

8. The results from the present study could serve as a guideline for the choice of open distal anastomosis under hypothermic circulatory arrest with bilateral selective antegrade cerebral perfusion and mild-to-moderate hypothermia in every patient with acute type A aortic dissection.

IX. List of publications related to the dissertation.

1. Gegouskov, V., **Manchev, G.**, Danov, V., Stoitsev, G., Iliev, S. *Direct cannulation of ascending aorta versus standard femoral artery cannulation in acute aortic dissection type a.* Heart Surgery Forum, 21(3), pp. E139–E144; ISSN: 1098-3511; (Web of Science, Scopus)

2. G. Manchev, B. Markov, S. Petrov, V. Gegouskov. *Repeated Recurrence of a Left Atrial Myxoma: a Case Report*. International Journal of Scientific Research, 2015, 4(2): 277-278; ISSN: 2277-8179

3. Данов В., **Манчев Г.**, Стоицев Г., Гегусков В. *Реоперативен случай на пациент със синдром на Марфан.*, Списание МД, 2015, бр. 3 (87): 91-93; ISSN: 1312-4471

4. <u>Г. Манчев</u>, В. Горановска, Х. Николов, В. Гегусков. Инфекции на срединната стернотомия – насоки за превенция и лечение. [ОСЕМНАДЕСЕТИ] XVIII Национален Конгрес по хирургия с международно участие 06-08.10.2022 г. гр. Плевен, стр. 33-54; ISBN: 978-954-756-299-8.