Impact of cerebral protection strategy used during open surgical aortic arch replacement on visceral function

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Hiermit erkläre ich, die Dissertation mit dem Titel „Impact of cerebral protection strategy used during open surgical aortic arch replacement on visceral function" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

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ß	probability of type II error
AB therapy	antibiotic therapy
ACP	antegrade cerebral perfusion
add OP	additional operation
ANOVA	analysis of variance
Ao. rupture	aortic rupture
AP	alcalic phosphatase
Arch Rep	arch replacement
Art. hypertension	arterial hypertension
Asc. aorta	ascending aorta
ATP	adenosine triphosphate
AUC	area under the curve
AVR	aortic valve replacement
BMI	body mass index
BUN	blood urea nitrogen
DHCA	deep hypothermic circulatory arrest
CABG	coronary artery bypass surgery
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
Crea	creatinine
FET	frozen elephant trunk
FiO_2	fraction of inspired oxygen
FPP	fresh frozen plasma

GGT	gamma-glutamyltranspeptidase
GPT	glutamate-pyruvate transaminase
H^+	hydrogen ion
Hb	hemoglobin
H_2CO_3	hydrogen bicarbonate
CI	cardiac index
Htc	hematocrit
CO	cardiac output
ICU	intensive care unit
Intra-OP	intra-operative
K^+	potassium ion
LOS	length of stay
Lower E. Neurology	lower extremity neurology
LV-EF	left ventricular ejection fraction
N	number of patients
Na^+	sodium ion
NaBic	sodium bicarbonate
NAG	N-acetyl-β-d-glucosaminidase
NIRS	near-infrared spectroscopy
p	p-value
PC	platelet concentrate
pCO_2	partial pressure of carbon dioxide
PEEP	positive end-expiratory pressure
Perf.	perfusion
P insp	pressure inspiratory
PICCO	pulse contour cardiac output

pO2	partial pressure of oxygen
POD	post-operative day
post-OP	post-operative
PPSB	prothrombin complex concentrate
PRBC	packed red blood cells
Pre-OP	pre-operative
Prev. Sternotomy	previous sternotomy
RCP	retrograde cerebral perfusion
RR sys	systolic blood pressure
RR diast	diastolic blood pressure
SaO2	oxygen saturation
SCP	selective cerebral perfusion
SD	standard deviation
SEM	standard error of the mean
SPSS	Statistical Package for the Social Sciences, (SPSS Inc., Chicago)
T	temperature
TRIS	tris(hydroxymethyl)aminomethane
Upper E. Neurology	upper extremity neurology

1 Introduction

Ascending and transverse aortic arch aneurysms represent the great majority of aortic pathology (Lemole 1995) and are usually repaired through median sternotomy and under a short period of circulatory arrest. Numerous and diverse techniques of aortic arch replacement have been previously described (Bachet et al. 1991; Borst et al. 1988; Danner et al. 2007; Griepp et al. 1975; Kazui et al. 2001; Kouchoukos et al. 2001); and they depend on the morphologic characteristics of the disease on one side and of the personal preferences of the surgical team, the local clinical habits and experience on the other side.

All techniques include the performance of three anastomoses: a proximal anastomosis to the ascending aorta, a distal anastomosis to the descending aorta and the arch anastomosis (singular or multiple) to the supra-aortic vessels.

1.1 Open Surgical Aortic Arch Replacement

The "traditional method" for total aortic arch replacement, that was described by Griepp (Griepp et al. 1975) and popularized by Crawford and others (Crawford and Saleh 1981; Svensson et al. 1993) as the "distal aortic anastomosis first" technique, encompasses execution of the distal anastomosis and aortic arch anastomoses during the hypothermic circulatory arrest interval. The "elephant trunk" technique allows performance of second-stage descending aortic operations in case of disease progression such as an evolving aneurysm or chronic dissection (Schepens et al. 2002; Kieffer et al. 2000). The hybrid techniques - called "frozen elephant trunk" for Type A acute aortic dissection - in which the "elephant trunk" is replaced by a stent-graft deployed in the proximal descending aorta or in the distal arch could improve difficult repairs and broaden the indications for high-risk patients (Kato et al. 1996; Karck et al. 2003). The traditional "distal anastomosis first" technique still represents the gold standard associated with excellent outcomes (Bachet 2008).

However, the "arch first" technique including performance of the anastomosis between the graft and the brachiocephalic arteries first is thought to minimize the period of brain ischemia. This technique provides arterial brain perfusion without requiring direct cannulation and perfusion of the brachiocephalic arteries (that could potentially result in embolization and stroke) (Kouchoukos et al. 2001).

Total replacement with "the proximal-first" technique is usually performed through a median sternotomy. The technique also allows immediate proximal repair during the cardiac arrest and the cooling period. In addition, antegrade cerebral perfusion can be immediately initiated and arch reconstruction performed before circulatory arrest. The circulatory arrest time is significantly reduced and needed only for the performance of the distal aortic anastomosis. Besides reducing both, myocardial ischemia and cerebral perfusion time (Tominaga et al. 2002), "the proximal-first" technique is simpler to perform and associated with fewer complications (Tominaga 2008). This technique should be considered for total aortic arch replacement, especially when extensive aortic root reconstruction is necessary.

1.2   Cerebral Protection

Adequate cerebral protection during aortic arch surgery is considered crucial for outcome. Continuous brain perfusion have succeeded in decreasing the incidence of neurological complications (Tchervenkov et al. 2001; Pigula et al. 2000), however organ and system injury due to lack of perfusion below the aortic arch remains unclear. Whereas peripheral malperfusion was reported to contribute to poor prognosis after surgical aortic arch repair (Chiu and Miller 2016), visceral malperfusion caused by direct occlusion or circulatory arrest was shown to independently increase the risk for early and late mortality (Patel et al. 2008). Exposure to cardiopulmonary bypass, temperature changes and whole body ischemia/reperfusion may also trigger perturbations in the homeostatic, inflammatory and oxidative stress pathways that may further result in systemic inflammatory response syndrome and its progression to multiorgan failure. Sustained metabolic debt and multiorgan failure may contribute to post-operative morbidity and mortality after aortic arch surgery despite the progressive surgical techniques and improved neurological monitoring. Deeper hypothermia during circulatory arrest (Griepp et al. 1975), perfusion of the left subclavian artery, drainage of spinal fluid (Matsumura et al. 2009) and the use of a stent-graft matching the patients' anatomy, could secondarily prevent visceral malperfusion by preservation of collateral circulation.

The optimal brain protection technique during total replacement of aortic arch has not been clearly established. The objective of all current cerebral protection methods is prevention of cellular anoxia and acidosis and reduction of the energy requirements to the minimum necessary to maintain cellular viability in order to maintain the integrity of the central nervous system while the cerebral blood flow is interrupted. Deep hypothermia,

antegrade cerebral perfusion and retrograde cerebral perfusion are established tools of cerebral protection during circulatory arrest.

Initially, it has been emphasized that deep hypothermia alone could adequately protect the brain and viscera during brief periods of circulatory arrest, thus, enabling aortic replacement without perfusion (Urbanski et al. 2012). Indeed, **deep hypothermic circulatory arrest (DHCA)** reduces metabolic demands and oxygen consumption of the brain and the viscera and thus increases tolerance to hypoxia (Lewis and Taufic 1953; Elefteriades 2010). However, the DHCA technique provides only a restricted time to the surgeon to finish the aortic repair (Lai et al. 2002). It was shown that a 18°C core temperature may theoretically allow a safe DHCA for 45 to 60 minutes, but prolonged DHCA times exceeding this limit would increase the incidence of adverse neurologic outcome (Moon and Sundt 2002a; Svensson et al. 1993). However, complex arch pathology may require longer periods of safe arrest then that provided by DHCA only.

Retrograde cerebral perfusion (RCP) through the superior vena cava was first described in 1980 by Mills and Ochsner (Mills and Ochsner 1980), as a tool for the "emergency treatment for massive air embolism during cardiopulmonary bypass (CPB)". Later Lemole et al. (1982), (Lemole 1995; Bavaria et al. 2001) reported RCP as a cerebral protective technique during the surgical repair of aortic dissections. RCP could reduce the ischemic damage caused by DHCA alone (Bonser and Harrington 2008) and induce a beneficial washout of toxic ischemia-related excitatory amino acids and metabolites (Baumgartner et al. 1997; Tseng et al. 1999). While most of the studies focused on determining the neurologic effects of the technique, little is known about the impact of RCP on abdominal viscera.

Antegrade cerebral perfusion (ACP) pioneered by Kazui and Bachet (Kazui 2001; Bachet et al. 1991), in which the brain is selectively perfused through the right axillary or subclavian artery or by direct carotid and brachiocephalic cannulation, has been wildey used for elective aortic arch procedures (Okita et al. 2001; Strauch et al. 2004). ACP is physiologically superior to DHCA with or without RCP because it supplies sufficient oxygenated blood to the brain, thus maintaining the physiological brain energy metabolism (Sakurada et al. 1996). Several clinical studies have shown improved results regarding survival and neurologic outcomes using ACP compared to historical reference data (Kazui et al. 2001; Sanioglu et al. 2008; Etz et al. 2008). Moreover, ACP significantly reduced post-operative length of stay (LOS) in the ICU accompanied with less renal dysfunction and improved survival when compared with DHCA (Di Eusanio et al. 2003). Algra et al.

(2012a) suggested that a partial perfusion of the viscera through collaterals during ACP (Andropoulos et al. 2003; Ly et al. 2011; Miyaji et al. 2010; Pigula et al. 2001) may be responsible for the improved outcome. Evidence of regional blood flow has been also reported in the abdominal or femoral arteries during ACP (Andropoulos et al. 2003; Ly et al. 2011; Pigula et al. 2001). However, the eventual protective effect of ACP on abdominal organ function remains speculative.

1.3   Visceral Malperfusion

Malperfusion of the abdominal organs is known to be a devastating complication of type A aortic dissection per se. Approximately one-third of acute Stanford type-A aortic dissection patients manifest pre-operative malperfusion syndrome (Bonser et al. 2011; Immer et al. 2006; Geirsson et al. 2007; Girdauskas et al. 2009) of various organ systems, and it is well-known that end-organ malperfusion has the potential to dramatically decrease the chance of successful outcome. Pacini et al. (2013) reported a 2.4 % incidence of mesenteric malperfusion and found an associated hospital mortality as high as 70%. Whereas visceral malperfusion associated with acute aortic dissection has an incidence of 3%-5%, patients with intestinal ischemia have an operative mortality rate ranging from 43% to 87% (Fann et al. 1990; Apaydin et al. 2002). In consent, multivariate analysis also confirmed mesenteric malperfusion to be an independent risk factor for mortality (Pacini et al. 2013). Whereas single-organ malperfusion is associated with a mortality rate of 34.7%, two organ system involvement increases mortality up to 61.9%. In the presence of three or more organ system malperfusion the mortality rate was reported to rise to 85.7% (Pacini et al. 2013).

The real effect of various perfusion strategies on cerebral protection and operative mortality has not yet been clearly outlined (Goldstein et al. 2001; Moon and Sundt 2002b; Ehrlich et al. 2000; Hagl et al. 2001). Several studies (Oudemans-van Straaten et al. 1996; Tsunooka et al. 2006; Dong et al. 2009) revealed the susceptibility of the intestine to microcirculatory perfusion in the setting of cardiac surgery, showing an association with intestinal barrier dysfunction, bacterial translocation and neutrophil infiltration.

Organ-specific biomarkers are able to estimate the degree of visceral injury at an early post-operative time point (Zierer et al. 2007; Andrási et al. 2014). Neutrophil gelatinase-associated lipocalin is the most widely described marker for renal injury; however, kidney injury molecule-1, liver fatty acid binding protein, intestinal fatty acid binding protein, glutathione s-transferase and N-acetyl-β-D-glucosaminidase have been also reported

(Thuijls et al. 2011; Derikx et al. 2007; Liang et al. 2010; Krawczeski et al. 2011; Askenazi et al. 2011; Du et al. 2011). However, in the emergency life-saving non-elective setting of dissection, the realization of a prospective study for the establishment of new laboratory markers remains difficult. Moreover, in cases where pre-operative damage is present the relative change of these markers is difficult to be interpreted. Nevertheless, renal biomarkers (Liang et al. 2010; Krawczeski et al. 2011; Askenazi et al. 2011; Du et al. 2011; Waikar et al. 2010) confirmed that DHCA results in more renal injury than ACP.

More recent studies (Algra et al. 2012a; Algra et al. 2012b) suggest that ACP might provide more abdominal perfusion than does DHCA via the collateral circulation granted by the perfusion of the left subclavian arteries. Consequently, this seems to have a protective effect on the viscera.

1.4   Aim of the Work

To date, there is no consensus among surgeons dealing with large volumes of aortic arch pathologies on the best visceral protection strategy.

It remains further unclear whether post-operative visceral malperfusion is depending on and consequently might be influenced by the intra-operative perfusion management or rather remains a hallmark of the pre-operative status.

The clinical effects of current methods of brain protection (DHCA, RCP and ACP) on the post-operative visceral function in conditions of pre-operatively present malperfusion remained unexplored.

The purpose of the current investigation is:

1) to determine how different approaches of cerebral protection used at our institution during the last two decades influenced operative mortality, clinical outcome and long-term survival after open surgical aortic arch replacement;

2) to establish relationships to visceral organ dysfunction;

3) to report on the influence of type of disease, type of procedures and the role of additional procedures on the post-operative visceral dysfunction;

4) to evaluate the effect of pre-operative visceral ischemia on the post-operative development of malperfusion syndrome;

5) to identify biochemical markers and analyze clinical outcome that would support the theory of improved visceral protection offered by the use of antegrade selective cerebral perfusion.

2   Material and Methods

Retrospectively, data was collected by medical chart review from all consecutive adult patients who underwent aortic arch replacement with the use of deep hypothermic circulatory arrest between June 2005 and March 2016 at the Department of Thoracic, Cardiac and Vascular Surgery, University Medical Center of Göttingen, Germany. An institutional ethics review board's approval was obtained for the collection and analysis of the data in a retrospective fashion (No. 2-10-17). The need for informed consent was waived.

2.1   Patient Population

Between June 2005 and March 2016, 128 consecutive adult patients with acquired aortic arch disease underwent for the first time open surgical aortic arch replacement under circulatory arrest at the Department of Thoracic, Cardiac and Vascular Surgery, University of Göttingen, Germany. Patients with congenital diseases or requiring repeated aortic arch replacement were excluded from the present study. The patients were retrospectively divided into 3 main groups according to whether they did have deep hypothermic circulatory arrest without additional cerebral perfusion (DHCA), did have selective antegrade cerebral perfusion (ACP) or did have retrograde cerebral perfusion (RCP). DHCA was applied in 37 patients, ACP in 70 patients and RCP in 21 patients.

2.2   Anesthetic Protocol and Medication

Before anesthesia and surgery antihypertensive therapy with beta-blockers was applied first, before other vasodilators, if necessary. Right radial arterial pressure monitoring was instituted before induction of anesthesia.

Anesthesia was induced by sufentanil, followed by a hypnotic (mostly midazolam or etomidate) and muscle relaxation was provided with pancuronium or rocuronium. During the procedure anesthesia was maintained with sufentanil and a volatile anesthetic – mostly sevoflurane.

The alpha-stat method was used to carry out pH balance control in all patients. Aprotinin administration was rare. Arterial pressure was usually measured on the left radial artery. Regional oxygen saturation in the bilateral frontal lobes with near-infrared spectroscopy

was usually used for cerebral monitoring. Pharmacologic neuroprotection was not performed.

Blood pressure deviations were corrected with norepinephrine and nitroglycerine in both groups. In order to maintain an adequate perfusion pressure and cardiac output, mean arterial pressure was held between 60 mmHg and 70 mmHg by administration of volume, and optimization of heart rate and rhythm. Inotropic support was started with dobutamine or epinephrine. Blood sampling was routinely performed and registered during the operations.

2.3 Surgical Procedure and Type of Cerebral Protection

All patients underwent median sternotomy. Cardiopulmonary bypass (CPB) was instituted after heparinisation. The arterial cannula was placed in the ascending aorta or the femoral artery and a venous single 2-stage cannula in the right atrium. Left ventricular venting was always perfomed through a vent placed through the right superior pulmonary vein. Myocardial protection was achieved with cold crystalloid cardioplegia and topical pericardial cooling (Di Eusanio et al. 2002).

After completion of the aortic procedure, warming was carried out by means of CPB until a rectal temperature of 35°C was achieved, limiting the gradient between CPB blood and body temperature to less than 10°C, and a maximal warming temperature of 37°C. (Reich et al. 1999).

2.3.1 Deep Hypothermic Circulatory Arrest

Profound hypothermia was achieved by cooling on CPB. During the cooling period of 30 to 40 minutes, the proximal aortic anastomosis was usually performed. When a core temperature of 18°C was achieved, circulation was arrested and the distal repair was carried out. The head was packed in ice to prevent warming of the central nervous system.

2.3.2 Antegrade Cerebral Perfusion

The cannulation techniques during ACP with moderate hypothermic circulatory include arterial cannulation through the subclavian artery with or without femoral cannulation (Di Eusanio et al. 2002; Dossche et al. 2000). Cooling is performed on CPB to achieve a core temperature of 18°C to 22°C, then the systemic circulation can be arrested and the aneurysm opened. Cerebral perfusion cannulas were then inserted into the innominate and

left common carotid arteries through the aortic lumen, while the patient was positioned in the Trendelenburg position and connected to the oxygenator with a separate single-roller pump head. The left subclavian artery may be clamped or occluded to avoid the steal phenomenon. Cerebral perfusion was adjusted to maintain a right radial arterial pressure between 40 and 70 mm Hg as described by Di Eusanio et al. (2002). Circulatory arrest was instituted during the open performance of the distal anastomosis.

2.3.3   Retrograde Cerebral Perfusion

RCP was applied through an arteriovenous shunt to a superior vena cava cannula (28F to 32F) after bicaval cannulation as described by Zierer et al. (2007). RCP was initiated at 100 mL/min and increased to 300 to 500 mL/min. The innominate vein pressure (central venous pressure) was kept below 20 to 25 mm Hg. Dark blood was verified emanating from the brachiocephalic orifices in all patients. The temperature of inflow blood during RCP was 10°C (Zierer et al. 2007).

2.4   Data Collection Protocol

Demographic and clinical data have been collected from the medical charts. Operative and ischemic times as well as type of the operations and their extension have been collected from the surgical operation chart. Pre-operative and post-operative hemodynamic data, ventilation parameters, data obtained from arterial blood gas analyses and intra-operative catecholamine support, as well as intra-operative transfusion and pharmacologic optimization of coagulopathy were also quantified. Hemodynamic and ventilatory parameters, arterial and venous blood gas analysis, catecholamine support, laboratory visceral markers, extent of the post-operative pharmacologic and mechanical support as well as renal replacement therapy and the need for surgical revision were extracted from the intensive care therapy and stationary evaluation charts.

Hemodynamic instability was defined as a state where the circulatory system is not able to provide adequate perfusion of the tissues due to hypovolemic, distributive, cardiogenic or obstructive factors (Sevransky 2009). Patients requiring fluid and inotropic resuscitation to maintain mean arterial blood pressure above 65 mmHg are considered hemodynamically instable (Sevransky 2009).

2.5 Pre-operative Clinical and Demographic Data

The following demographic and clinical data were collected pre-operatively: age, gender, risk factors (body mass index, hypertension, diabetes mellitus, smoking, ejection fraction, chronic obstructive pulmonary disease (COPD), renal replacement therapy and renal dysfunction), renal function variables (serum creatinine, serum urea, estimated creatinine clearance and hematocrit), urgency of surgery, associated surgical procedures (such as coronary artery bypass grafting, valve surgery, combined aortic root procedures).

2.6 Hemodynamic Parameters

Systolic and diastolic systemic as well as central venous pressure were registered intra- and post-operatively. Cardiac output monitoring was provided in high-risk catecholamine-dependent patients during the intensive care stay.

2.7 Catecholamine-, Transfusion- and Coagulation Therapy

The following values were collected during the operation and during the post-operative period from the medical charts: inotropic substitution (epinephrine, norepinephrine, dopamine, dobutamine, enoximone; transfusion of red blood cell (PRBC), fresh frozen plasma (FFP), platelet (PC); substitution of prothrombin complex concentrate usage (PPSB) and fibrinogen; and buffering with NaBic and TRIS.

Inotrope scores were calculated using the following formula ($\mu g.kg^{-1}.min^{-1}$): dopamine + dobutamine + ($15 \times$ enoximone) + ($100 \times$ epinephrine) + ($100 \times$ norepinephrine) (Chen et al. 2006).

2.8 Intensive Care Treatment

Duration of mechanical ventilation, requirements and duration of renal replacement therapy, catecholamine support, buffer substitution and AB therapy were quantified during the ICU stay.

2.9 Blood Gas Analysis and Abdominal Biomarkers

Values of Hemoglobin (Hb), PO_2, PCO_2, SO_2, H_2CO_3, pH, lactate and electrolytes measured in the arterial blood with a Blood Gas Analyzer before and after the operation and during the intensive care stay were extracted from the charts.

Hepatocellular injury was evaluated through GPT and GGT. Gastrointestinal damage was evaluated through alkaline phosphatase, bilirubin, lactate and creatine kinase levels. Renal function was evaluated by creatinine and blood urea nitrogen.

2.10   Post-operative Outcome

To further characterize post-operative outcomes, length of ICU stay, hospital stay and in-hospital death were extracted. Intra-operative mortality, 48h mortality, 30 days mortality and in-hospital mortality were determined to evaluate the influence of type of circulatory support and establish potential interactions with abdominal organ function.

2.11   Statistical Analysis

Continuous variables are expressed as mean ± standard error of the mean (mean ± SEM). Student t-test for independent samples was used followed by Fisher exact test when needed. Categorical variables are presented as number (%). In univariate analysis, categorical data was analyzed by square or Fisher exact tests and continuous data were analyzed by using t-test or Wilcoxon rank sum tests, as appropriate (Hong et al. 2017). Changes in parameter over the time were tested using repeated measures analysis of variance (ANOVA) followed by paired Student t-test. Differences among corresponding parameters of the three treatment groups were compared using one-way ANOVA. The power of a test was defined as 1-ß, where ß represented the probability of a type II error. A test is considered significant when the probability of type II error ß is less than 0.20 and thus, the power of the test higher than 80%. The statistical analysis was performed using SPSS version 10.0 software (SPSS Inc., Chicago, IL). A two-tailed P-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Pre-operative Evaluation

3.1.1 Demographic Data

There were no significant differences between the three groups of patients in term of demographics, risk factors, heart function and previous heart surgery (Table 1).

3.1.2 Clinical and Imaging Characteristics of the Aortic Disease

With respect to the clinical presentation, patients suffered mainly from thoracic pain and the majority of them was hemodynamically stable (Table 2) in all three groups. Interestingly, pre-operative abdominal pain was not assessed in any of these patients. This finding could be explained by the fact that no complete occlusion of all three visceral arteries was present on the pre-operative CT-scan in none of the cases. More than 70% of the patients in each group were suffering from acute dissection involving the aortic arch, however, rarely showing true lumen collaps at abdominal level (29.7%, 33.3%). No other significant differences in terms of disease extension were assessed between the groups (Table 3).

3.2 Intra-operative Evaluation

3.2.1 Operative Characteristics and Surgical Revisions

Whereas venous cannulations sites were similar between groups, subclavian artery cannulation was mostly used in the antegrade perfusion group (Table 4). Total arch replacement was almost always performed in the retrograde perfusion group, but only in the 60% of the cases operated without selective cerebral perfusion. Total arch replacement was almost always performed in the RCP group (95.2%, $p = 0.026$ vs. ACP and DHCA); but in less percent in the DHCA (64.9%) and ACP (74.3%) groups; however, without significant differences between the DHCA and ACP groups.

Table 1. Demographic data

	DHCA	ACP	RCP	P-value
Nr. of Patients	37	70	21	
Age (Mean ± SD)	63.6 ± 11.9	61.3 ± 11.4	61.4 ± 10.6	0.902
BMI (Mean ± SD)	28.3 ± 4.4	27.1 ± 4.4	26.9 ± 5.3	0.837
Male Gender (%)	67.6	62.9	76.2	0.525
Art. Hypertension (%)	83.8	87.1	80.9	0.759
Smoking (%)	16.2	17.1	23.8	0.738
Diabetes mellitus (%)	13.5	12.9	14.3	1.0
Renal Disease (%)	21.6	24.3	9.5	0.385
COPD (%)	8.1	7.1	9.5	0.905
LV-EF (Mean ± SD of %)	54.7 ± 11.9	51.9 ± 74.2	48.3± 14.5	0.739
Prev. Sternotomy (%)				
Valve Surgery	5.4	10.0	9.5	0.687
CABG	2.7	4.3	0.0	1.0
Aortic Surgery	2.7	1.4	4.8	0.577

Legends for Table 1, Table 2, Table 3, Table 4: DHCA, circulatory arrest; ACP, antegrade cerebral perfusion, RCP, retrograde cerebral perfusion; BMI = body mass index; art. Hypertension, arterial hypertension; COPD = chronic obstructive pulmonary disease; LV-EF = left ventricular ejection fraction; prev. Sternotomy, previous sternotomy; CABG = coronary artery bypass surgery, Pericard. Effusion (T), pericardial effusion (Tamponade); contained Ao. Rupture, contained aortic rupture; Asc. Aorta, ascending aorta; Replac., replacement; AVR, aortic valve replacement. P < 0.05 is statistically significant.

Table 2. Clinical status

	DHCA	%	ACP	%	RCP	%	P-value
Nr. of Patients	37	%	70	%	21	%	
Symptoms							
Thoracic Pain	16	**43.2**	39	**55.7**	11	**52.4**	0.453
Cerebral Neurology	4	**10.8**	11	**15.7**	3	**14.3**	0.886
Upper E. Neurology	0	**0.0**	1	**1.4**	1	**4.8**	0.384
Lower E. Neurology	2	**5.4**	11	**15.7**	1	**4.8**	0.242
Hemodynamics							
Post-Resuscitation	1	**2.7**	4	**5.7**	2	**9.5**	0.504
Stable	34	**91.9**	59	**84.3**	16	**76.2**	0.261
Unstable	3	**8.1**	11	**15.7**	5	**23.8**	0.261

Table 3. Disease extension (CT-scan evaluation)

	DHCA	%	ACP	%	RCP	%	P-value
Nr. of Patients	37	%	70	%	21	%	
Arch Aneurysm	7	**18.9**	23	**32.9**	7	**33.3**	0.294
Aortic Dissection							
Ascending	29	**78.4**	50	**71.4**	16	**76.2**	0.759
Arch	31	**83.8**	52	**74.3**	16	**76.2**	0.545
Thoracic extension	18	**48.7**	35	**50.0**	9	**42.9**	0.859
Abdominal extension	11	**29.7**	22	**31.4**	7	**33.3**	0.966
Intramural Hematoma	0	**0.0**	7	**10.0**	0	**0.0**	0.066
Pericard. Effusion (T)	11	**29.7**	19	**27.1**	7	**33.3**	0.833
Contained Ao. Rupture	2	**5.4**	8	**11.4**	1	**4.8**	0.619
Free Aortic Rupture	0	**0.0**	2	**2.9**	0	**0.0**	0.681

Whereas the Yacoub procedure was applied in 19% of the RCP cases and was rarely used in the ACP cases, the Bentall procedure was the most preferred procedure for root repair and was additionally performed in approximately 30% of the cases of each group.

Aortic valve reconstruction and coronary revascularization was similarly performed in all groups (Table 4).

Table 4. Characteristics of the surgical techniques

	DHCA		ACP		RCP		P-value
Nr. of Patients	37	%	70	%	21	%	
Cannulation							
Asc. Aorta	9	**24.3**	18	**25.7**	4	**19.1**	0.885
Femoral Artery	28	**75.7**	32	**45.7**	16	**76.2**	**0.002**
Subclavian Artery	0	**0.0**	20	**28.6**	1	**4.8**	**0.00006**
Right Atrium	34	**91.9**	67	**95.7**	20	**95.7**	0.764
Femoral Vein	3	**8.1**	3	**2.9**	1	**4.8**	0.764
Aortic Approach							
Total Arch Replac.	24	**64.9**	52	**74.3**	20	**95.2**	**0.026**
Hemiarch Replac.	13	**32.4**	18	**25.7**	1	**4.8**	**0.026**
Additional Operation							
AVR	2	**5.4**	3	**4.3**	1	**4.8**	1.0
Bentall	11	**29.7**	21	**30.0**	8	**38.1**	0.756
David	0	**0.0**	2	**2.9**	0	**0.0**	0.681
Yacoub	0	**0.0**	5	**7.1**	4	**19.1**	**0.021**
CABG	7	**18.9**	12	**17.1**	1	**4.8**	0.355

Operation times were similar in all groups (Table 5); however, circulatory arrest group without selective perfusion had lower CPB- and circulatory arrest times. Conversely, the circulatory arrest group without perfusion required more often surgical revision than the groups where selective perfusion was used.

Surprisingly, no significant differences were assessed between the rates of surgical revision performed in the three groups (Table 5).

Table 5. Operative times and need for revision

	DHCA	ACP	RCP	P
Nr. of Patients	37	70	21	-
CPB (min)	295.5 ± 84.7	338.1 ± 126.1	345.0 ± 154.0	0.760
Cooling (min)	65.9 ± 21.5	74.0 ± 20.8	66.6 ± 18.3	0.804
Cardiac Arrest (min)	144.0 ± 37.0	164.0 ± 73.3	164.0 ± 61.0	0.848
DHCA/ACP/RCP (min)	52.0 ± 21.0	68.5 ± 29.1	66.8 ± 19.0	0.594
Rewarming (min)	123.4 ± 34.4	122.8 ± 30.9	99.6 ± 18.2	0.620
Operation (min)	425.9 ± 136.0	488.7 ± 175.3	474.5 ± 168.7	0.810
1 Revision (%)	14/37 **37.8%**	20/70 **28.6%**	4/21 **19.0%**	0.334
2 Revisions (%)	2/37 **5.4%**	3/70 **4.3%**	0/21 **0.0%**	0.839
3 Revisions (%)	0/37 **0.0%**	2/70 **2.9%**	0/21 **0.0%**	0.681

CPB cardiopulmonary bypass; DHCA/ACP/RCP, circulatory arrest time equaling antegrade and retrograde cerebral perfusion times in the ACP and RCP groups, respectively. $P < 0.05$ is statistically significant.

Only 1 of the total of 128 patients required laparotomy for hemicolectomy immediately after the aortic arch replacement because of extensive bowel necrosis, although antegrade cerebral perfusion and deep cooling had been used. This patient was pre-operatively

diagnosed with an aortic dissection Type A involving the aortic arch, but not the descending aorta. No clinical signs of abdominal ischemia have been found, however, the pre-operative contrast-enhanced computer tomography scan revealed thickened and edematous intestinal wall with fluid retention. Re-thoracotomy was required on the first post-operative days because of hemodynamic instability. Surgical closure of the sternotomy was performed on the fourth post-operative day. The patient died on the 39th post-operative day of multiorgan dysfunction.

However, the increased CPB- and cardiac arrest times (Table 5) seem to be related to the additional aortic root or cardiac reconstruction procedures rather than associated to the type of selective perfusion technique that was used (Figure 1).

The performance of additional cardiac procedures (presented in Table 4), significantly increased operation times, CPB times and cardiac arrest times in both antegrade and retrograde selective perfusion groups; however, without affecting cooling-, rewarming- and circulatory arrest periods (Figure 1).

Figure 1. Effect of additional cardiac and/or aortic root operation on the operative times
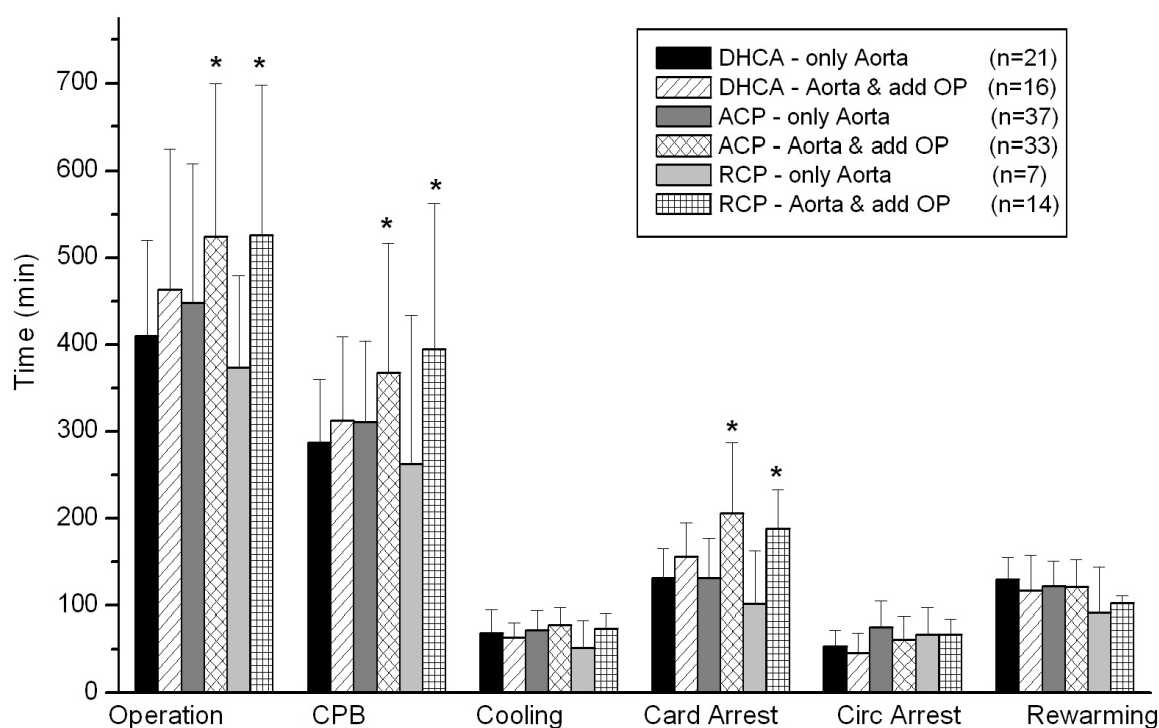
*, p< 0.05 Aorta & add OP vs only Aorta of the same cerebral protection group

3.2.2 Pharmacological Treatment

Different catecholamine and buffer solutions have been used intra-operatively. A lower proportion of patients in the RCP group required catecholamine therapy during the operation (Figure 2) when compared to ACP and DHCA groups. However, no significant differences between the intra-operatively applied catecholamine-quantities were found (Figure 3) between the groups.

Figure 2. Proportion of patients requiring intra-operative catecholamines and buffer
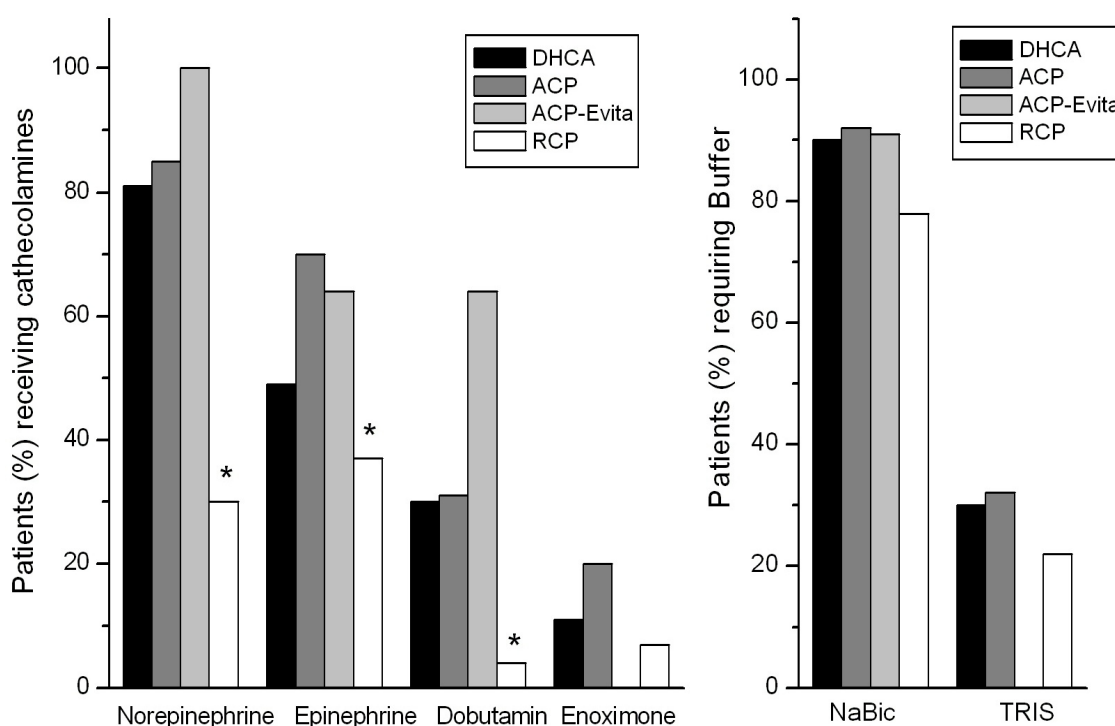
The percentage of patients requiring buffer and the quantities of buffer that have been administered did not differ between the groups (Figure 2, Figure 3).

At the beginning of the study period when mainly DHCA and RCP were used, transfusion of FFP was the main therapeutic tool for CPB-associated coagulopathy. More recently, when mostly ACP was applied, the availability of coagulation factors and thromboelastography diagnostic allowed selective application of coagulation factors thus, significantly reducing blood cells transfusion.

Figure 3. Intra-operative application of catecholamines and buffer

Figure 2, 3: DHCA, deep hypothermic circulatory arrest (n=37); ACP, antegrade cerebral perfusion without Evita grafts (n=59); ACP-Evita, antegrade cerebral perfusion with EVITA grafts (n=11), RCP, retrograde cerebral perfusion (n=21). *, p< 0.05 vs ACP

Further analysis of blood transfusion quantity revealed that higher transfusion was used for RCP technique (Figure 5). Whereas no significances have been determined between the intra-operative transfusions in the DHCA, ACP and RCP groups, ACP-Evita graft implantation required significantly less PC and FFP administration than the RCP. Moreover, DHCA required less PCs and coagulation factors than ACP and RCP. Whereas ACP-Evita received more coagulation factors, ACP with classic FET implantation was associated with more PRBC and PC administration usually treated with coagulation factors. These findings correspond to the evolution in the treatment of intra-operative coagulopathies.

Whereas all three main groups showed similar post-operative outcome in terms of blood gas analysis, the RCP group required more catecholamines and more blood products during the operation than the DHCA and ACP groups.

Figure 4. Proportion of patients requiring intra-operative blood replacement therapy
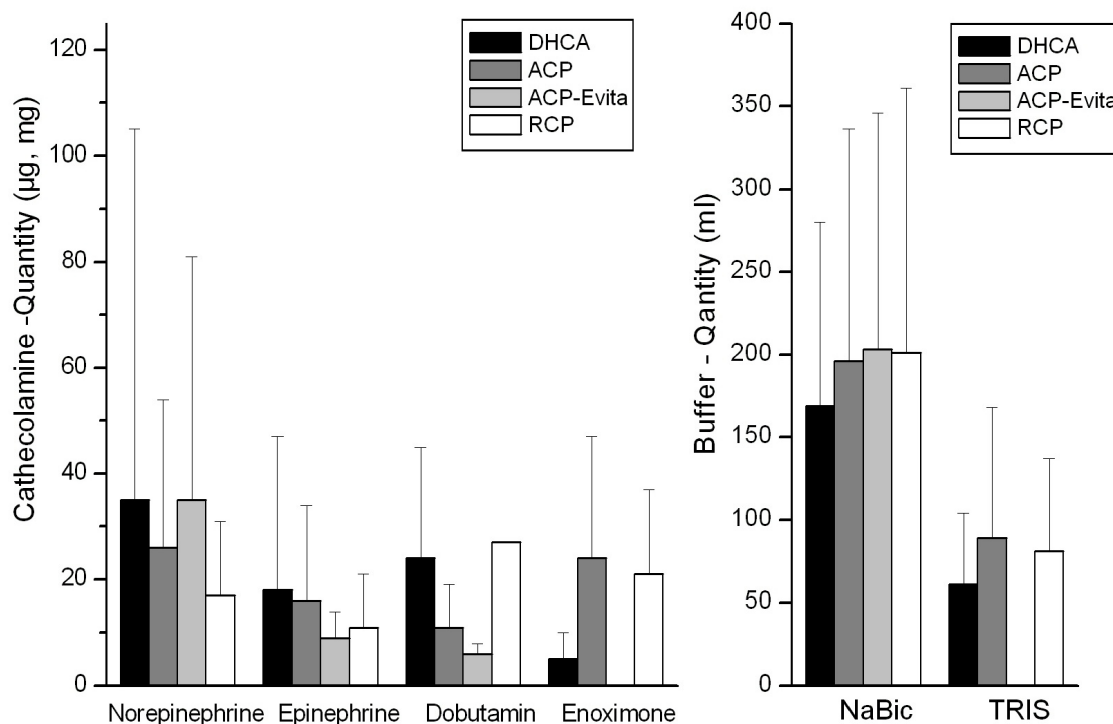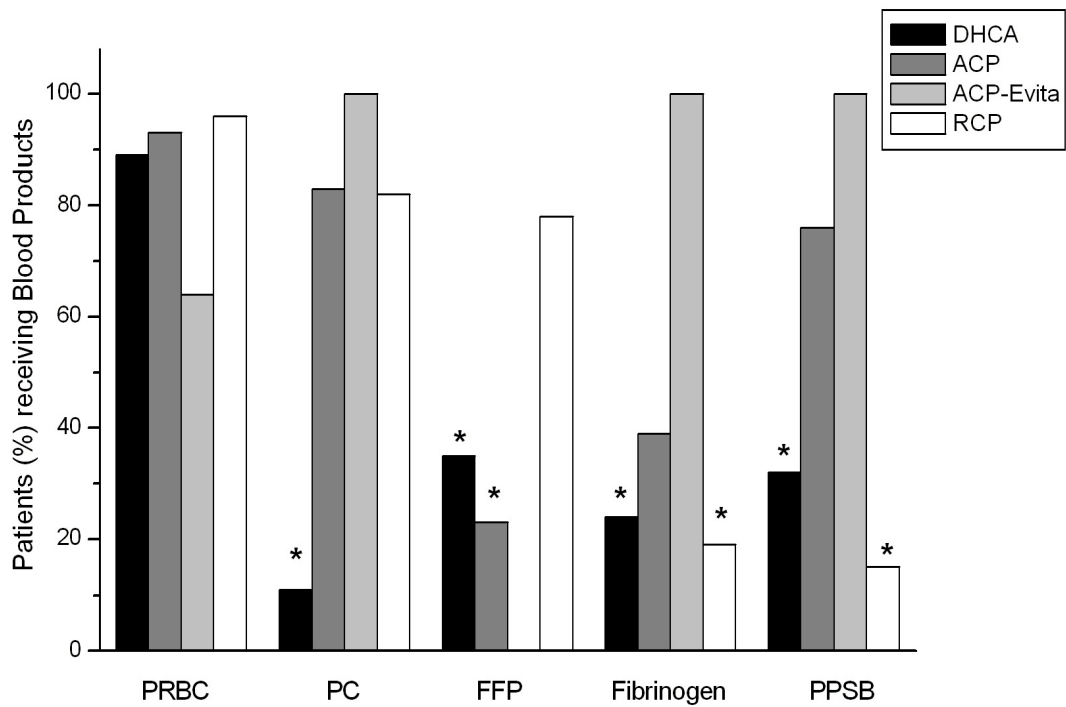

DHCA, deep hypothermic circulatory arrest (n=37); ACP, antegrade cerebral perfusion without Evita grafts (n=59); ACP-Evita, antegrade cerebral perfusion with EVITA grafts (n=11), RCP, retrograde cerebral perfusion (n=21). PRBC, packed red blood concentrate; PC, platelet concentrate; FFP, fresh frozen plasma; PPSB, prothrombin complex; *, p< 0.05 vs ACP-EVITA for PC, Fibrinogen, PPSB, and vs RCP for FFP.

Figure 5. Intra-operative administration of blood products
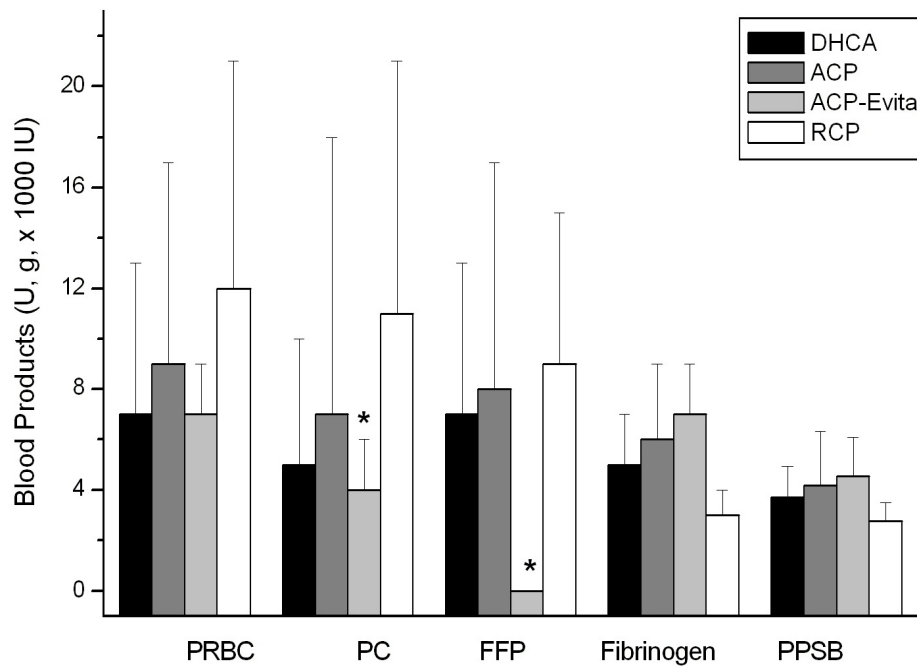
*, p< 0.05 vs RCP

3.2.3   Hemodynamics and Ventilation

Comparable hemodynamics and pulmonary function of the patients is mirrored by the similar ventilatory support and hemodynamic variables at the end of the operation (Table 6).

Table 6. Post-operative hemodynamics and ventilation (at the end of the operation)

	DHCA			ACP			RCP			P
Nr. of Patients	**37**			**70**			**21**			-
RR sys (mmHg)	96.9	±	17.3	98.1	±	24.2	100.4	±	26.4	0.909
RR diast (mmHg)	50.8	±	9.7	52.4	±	14.4	58.9	±	17.7	0.661
P insp	21.0	±	3.6	19.8	±	4.3	20.9	±	4.2	0.854
PEEP	6.8	±	1.7	6.3	±	1.6	7.0	±	2.2	0.823
FiO_2 (%)	0.9	±	0.3	0.9	±	0.2	0.9	±	0.2	0.948

Figure 6. Post-operative arterial lactate values in the subgroups (at the end of the operation)
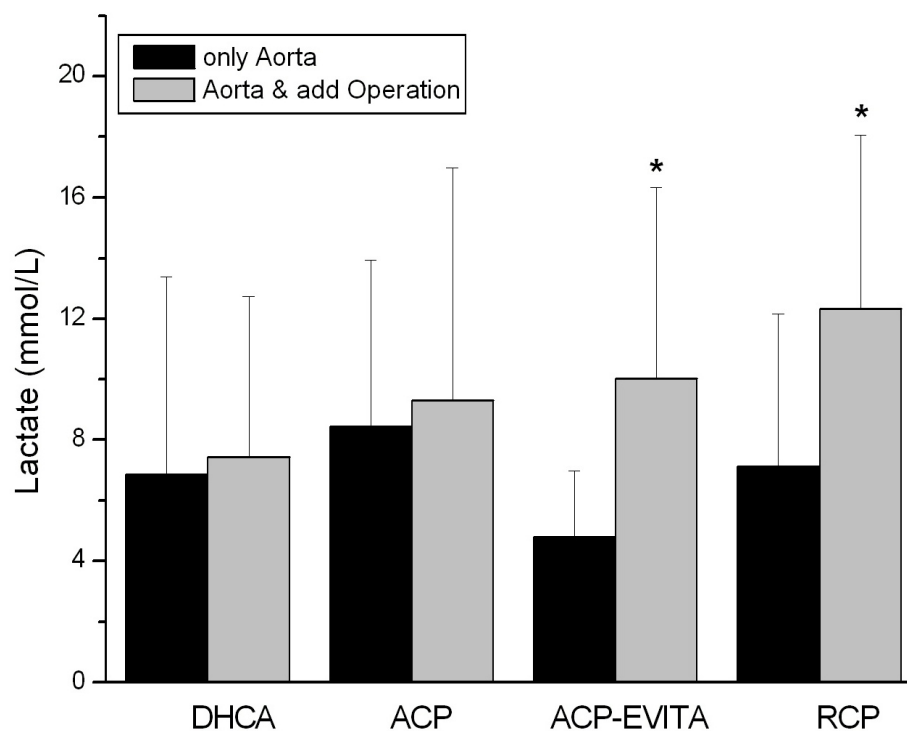
*, $p < 0.05$ Aorta & additional operation group vs only Aorta group

3.2.4 Blood Gas Analysis

The pre-operative (Table 7) and post-operative (Table 8) blood gas analysis revealed no differences between the groups. No significant differences were found between the blood gas values of the three main groups before the operation, however slightly higher lactate values were observed post-operatively in the ACP and RCP groups, without reaching the level of significance.

Whereas the lactate values were not influenced by the performance of additional cardiac operation in the DHCA and ACP subgroups (Figure 6), the use of the EVITA system tended to be associated with lower lactate values in the pure aortic surgery group. Lower lactate levels were found in the pure aortic groups operated with ACP-EVITA and RCP (Figure 6).

Table 7. Pre-operative blood gas analysis (at the beginning of the operation)

	DHCA	ACP	RCP	P
Nr. of Patients	37	70	21	-
pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	1.0
pO_2	164.8 ± 132.7	181.1 ± 133.8	189.8 ± 134.5	0.899
pCO_2	43.5 ± 3.6	43.4 ± 7.3	43.3 ± 11.9	0.984
SaO_2	94.9 ± 5.6	95.1 ± 11.6	95.2 ± 11.4	0.979
Hb	11.2 ± 2.6	12.2 ± 3.8	12.6 ± 1.9	0.709
Htc	37.1 ± 6.1	36.3 ± 7.0	36.7 ± 10.3	0.934
Base Excess	-2.4 ± 5.3	-1.5 ± 4.7	-2.9 ± 4.9	0.876
HCO_3	23.4 ± 3.6	24.1 ± 4.4	22.2 ± 3.8	0.819
K^+	3.9 ± 1.1	4.3 ± 3.5	3.9 ± 0.7	0.950
Lactate	2.8 ± 3.9	2.5 ± 2.9	2.8 ± 2.4	0.951

Table 6, Table 7, Table 8: RR sys, systolic blood pressure, RR dias, diastolic blood pressure; P insp., inspiratory oxygen pressure; $p < 0.05$ is statistically significant.

Table 8. Post-operative blood gas analysis (at the end of the operation)

	DHCA	ACP	RCP	P
Nr. of Patients	37	70	21	-
pH	7.34 ± 0.07	7.32 ± 0.11	7.33 ± 0.16	0.900
pO_2	274.7 ± 121.7	255.7 ± 148.9	253.6 ± 158.9	0.916
pCO_2	42.9 ± 8.3	42.8 ± 8.2	43.9 ± 15.9	0.949
SaO_2	99.4 ± 1.9	94.9 ± 18.3	95.5 ± 7.8	0.859
Hb	9.5 ± 1.4	10.9 ± 4.3	9.6 ± 1.5	0.821
Htc	28.7 ± 4.3	32.4 ± 13.8	29.4 ± 4.6	0.847
Base Excess	-2.6 ± 3.9	-4.4 ± 5.3	-4.5 ± 5.6	0.777
HCO_3	22.9 ± 3.5	21.7 ± 4.1	21.1 ± 5	0.764
K^+	4.2 ± 0.7	4.1 ± 0.7	4.0 ± 0.6	0.847
Lactate	6.3 ± 4.3	8.6 ± 5.7	10.8 ± 5.4	0.523

Table 6, Table 7, Table 8: RR sys, systolic blood pressure, RR dias, diastolic blood pressure; P insp., inspiratory oxygen pressure; $p < 0.05$ is statistically significant.

3.3   Post-operative Evaluation

3.3.1   Intensive Care Treatment

No significant differences in terms of intubation, renal replacement therapy and pharmacologic support have been post-operatively observed between the three groups (Table 9). Moreover, intra-operative cerebral perfusion did not influence the length of the post-operative mechanical ventilation (Table 10).

Table 9. Intensive care therapy

Nr. of Patients	DHCA		ACP		RCP		P
	25	days	52	days	12	days	-
Intubation-time	25	6.1 ± 15.0	52	5.4 ± 8.5	12	6.2 ± 7.7	0.965
Renal repl. therapy	9	6.2 ± 2.9	13	8.2 ± 6.1	2	9.5 ± 1.5	0.620
Buffer	18	2.3 ± 1.0	39	2.1 ± 0.6	4	1.5 ± 0.5	0.716
Catechol.	24	5.6 ± 8.2	51	4.4 ± 3.9	10	4.4 ± 4.1	0.880
AB Therapy	24	9.8 ± 18.5	51	7.7 ± 8.4	12	7.1 ± 7.3	0.920

Table 10. Mechanical ventilation times

Nr. of Patients	DHCA		ACP		RCP		P
	25	%	52	%	12	%	-
Ventilation < 24h	11	**44.0**	20	**38.0**	5	**42.0**	0.952
Ventilation 24h - 72h	6	**24.0**	12	**23.0**	1	**8.0**	0.615
Ventilation 4d - 10d	6	**24 .0**	14	**27.0**	3	**25.0**	1.0
Ventilation > 10 d	2	**8.0**	6	**12.0**	3	**25.0**	0.384

Data of patients surviving the intensive care stay; h, hours; d, days.

3.3.2 Hemodynamic Monitoring

In terms of cardiac function, only monitoring of the DHCA (n=11) and ACP (n=18) patients allowed CO and CI calculations. The data of the RCP patients could not be quantified because no monitoring was performed in this group. No significant differences were assessed between the DHCA and ACP groups (Figure 7).

Figure 7. Early post-operative cardiac function
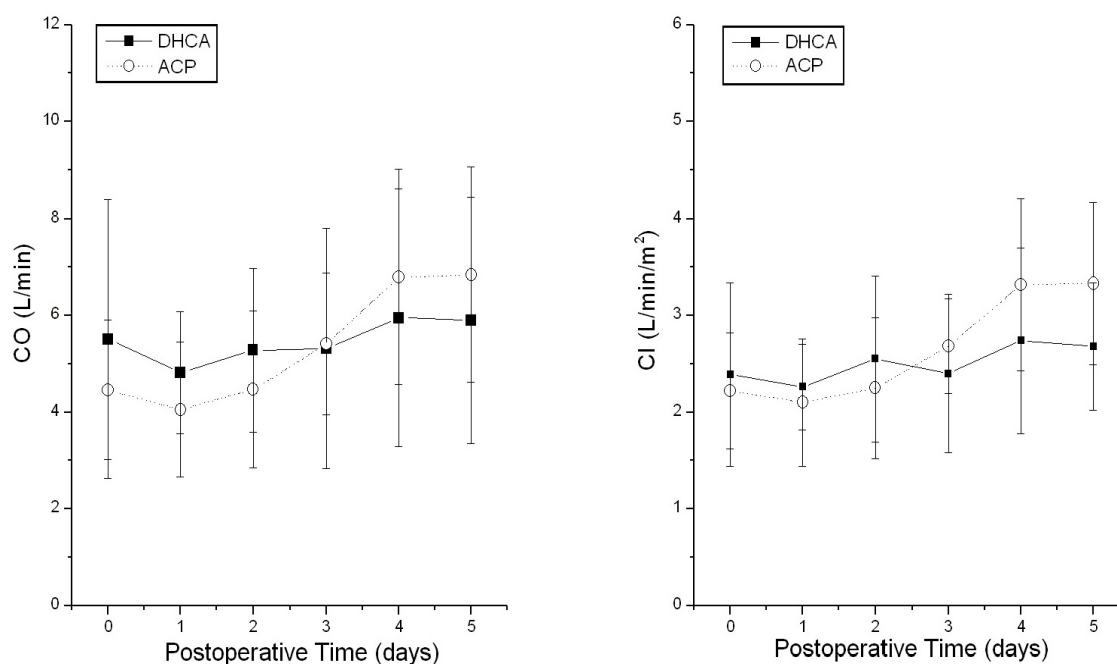
CO, Cardiac output; CI, cardiac index. Data were documented in 11 circulatory arrest and 21 antegrade cerebral perfusion patients. Mean ± SD values are represented.

3.3.3   Pharmacological Treatment

A significant difference was assessed between the amounts of catecholamine administered during the post-operative period.

As revealed by the catecholamine index calculations, both ACP and RCP patients required significantly less catecholamine support than DHCA patients during the first 30 post-operative days (Figure 8).

No significant difference in term of blood transfusion requirements, buffer or coagulation therapy was assessed between the groups (Figure 9). RCP patients receiving additional operations seem to require more transfusion post-operatively; however, these differences did not reach the level of significance (Figure 10).

The use of Evita system was not associated with lower need for transfusion or buffer administration during the post-operative period (Figure 10).

Figure 8. Post-operative catecholamine support
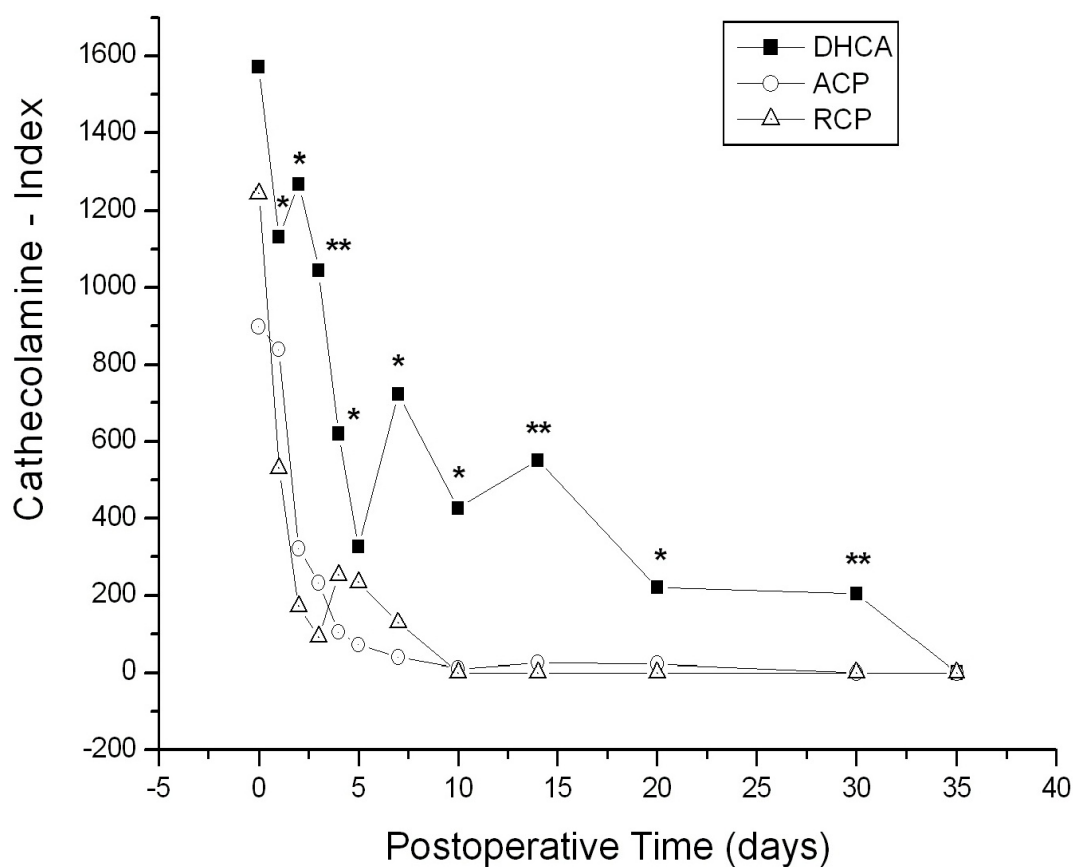
*, p< 0.05 , ** , p< 0.01 for circulatory arrest vs antegrade perfusion

3.4   Laboratory Analysis of Abdominal Markers

Whereas GPT was an early post-operative marker of hepatic damage, GGT remained unchanged in all groups during the first 5 post-operative days (Figure 11). Similarly, inflammation seems to be a delayed process that appears unchanged during the first 5 post-operative days and intensifies thereafter (Figure 12).

In terms of gastrointestinal ischemic injury, lactate values increase early during the pre-operative and intra-operative ischemia time, whereas CK appears to increase mostly after the reperfusion phase (Figure 13). Both changed relevantly in the early post-operative phase and returned to baseline levels after the 5th post-operative day.

Renal function markers increased progressively during the first 5 post-operative days and remained elevated almost in all cases during the entire hospital stay (Figure 14).

Figure 9. Incidence of post-operative blood replacement therapy (ICU)
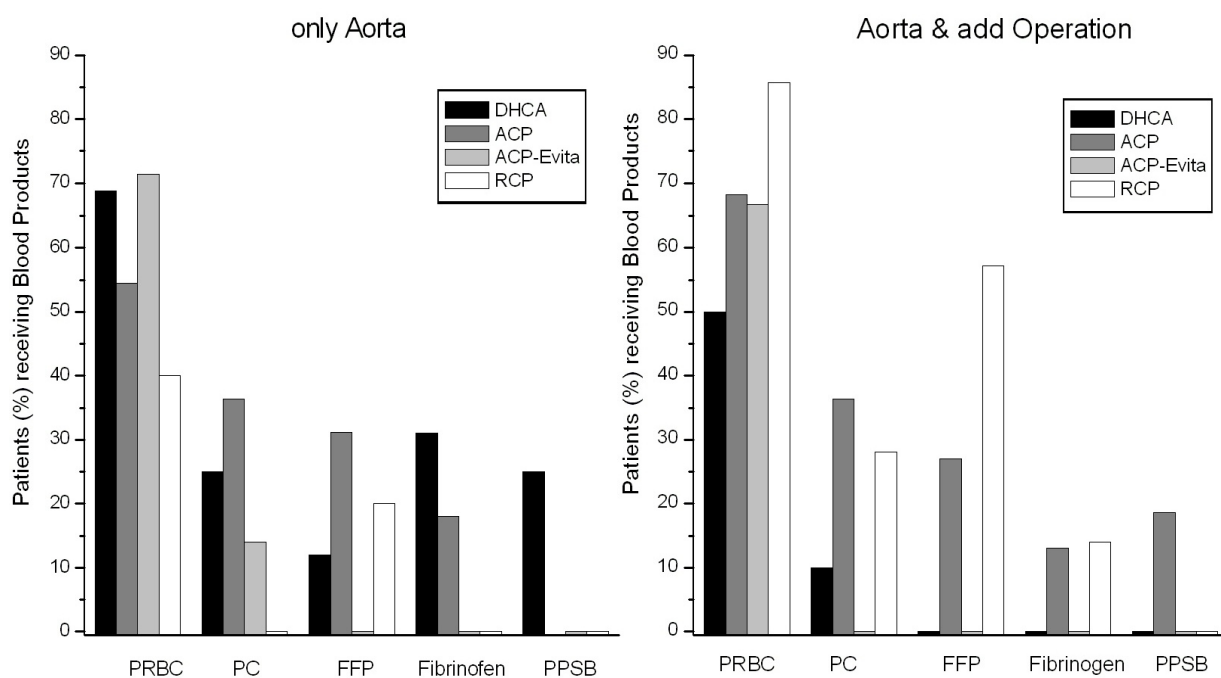
Figure 10. Magnitude of post-operative blood replacement therapy (ICU)
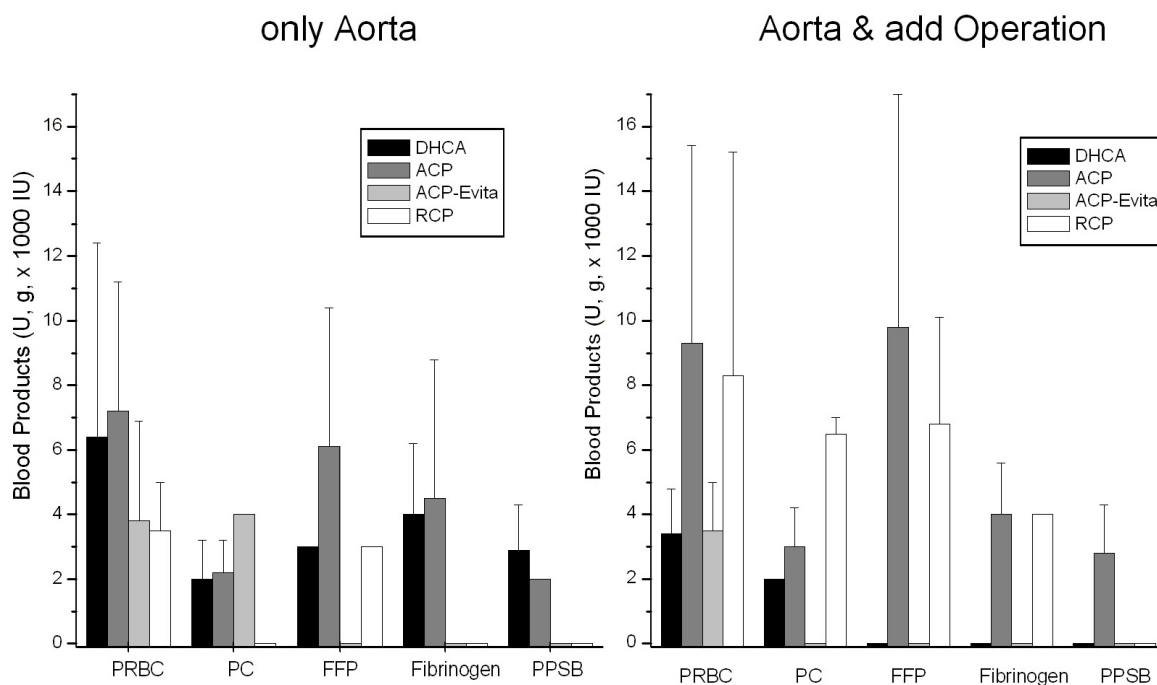
DHCA, deep hypothermic circulatory arrest (n=37); ACP, antegrade cerebral perfusion without Evita grafts (n=59); ACP-Evita, antegrade cerebral perfusion with EVITA grafts (n=11), RCP, retrograde cerebral perfusion (n=21). PRBC, packed red blood concentrate; PC, platelet concentrate; FFP, fresh frozen plasma; PPSB, prothrombin complex; *, p< 0.05 vs ACP-EVITA for PC, fibrinogen, PPSB, and vs RCP for FFP.

Figure 11. Markers of hepatic function
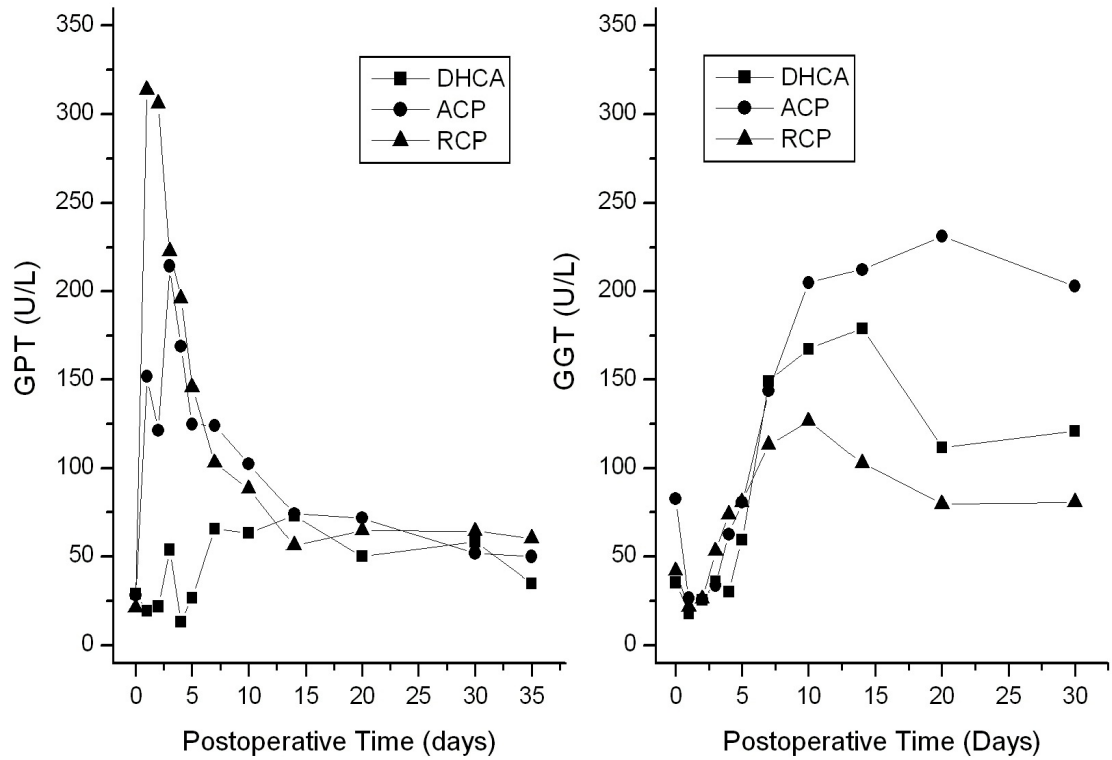
Figure 12. Markers of gastrointestinal inflammation
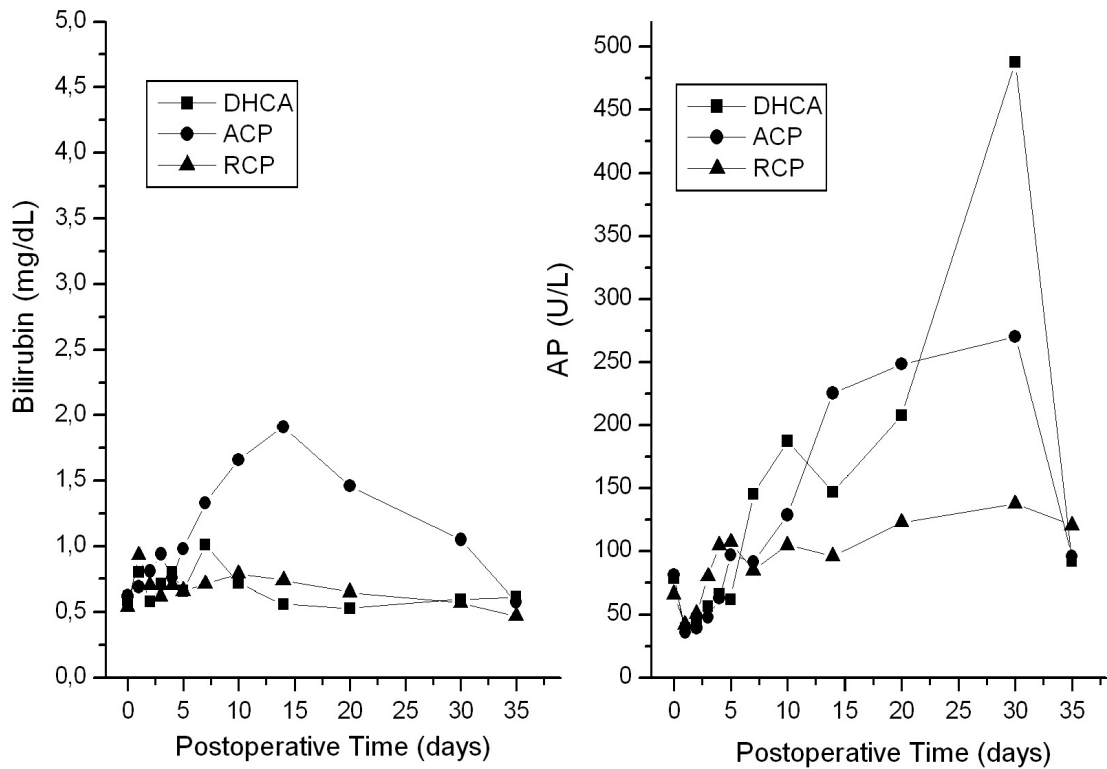
Mean values of laboratory parameters are represented. DHCA, deep hypothermic circulatory arrest (n=37); ACP, antegrade cerebral perfusion (n=70); RCP, retrograde cerebral perfusion (n=21).

Figure 13. Markers of intestinal ischemia/reperfusion injury
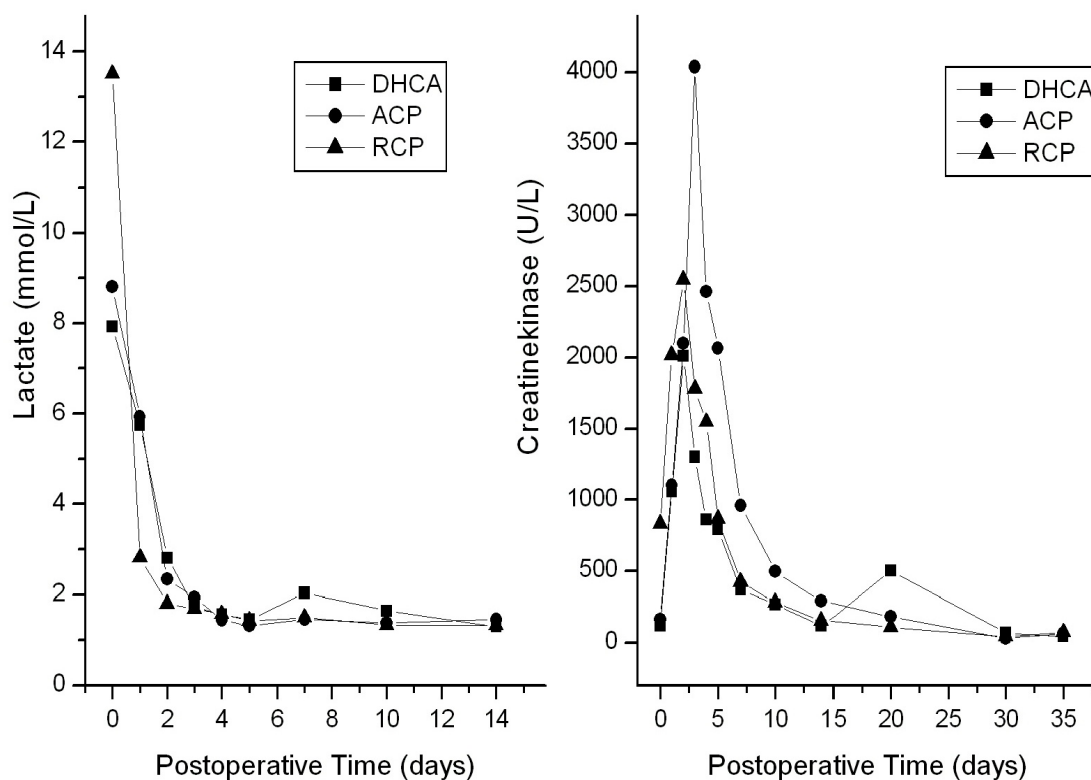
Figure 14. Markers of renal function
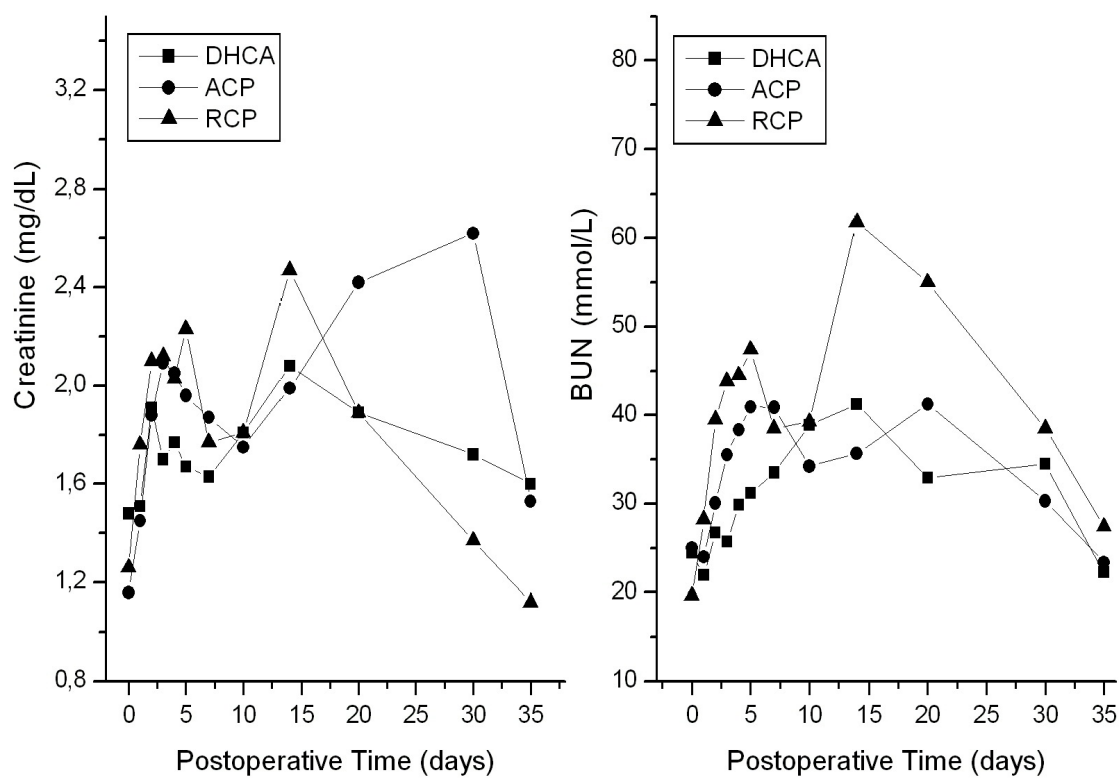
Mean values of laboratory parameters are represented. DHCA, deep hypothermic circulatory arrest (n=37); ACP, antegrade cerebral perfusion (n=70); RCP, retrograde cerebral perfusion (n=21).

Because of the heterogeneity of the three main groups and the small number of individuals protected by RCP, no significant differences for any of the markers could be revealed at any time during the evaluation.

3.5 Duration of Post-operative Care

The different types of circulatory support did not influence the intensive care therapy time or the hospital stay in our study (Figure 15).

Hospital stay (Figure 15) was comparable between the groups: 22.84±27.93 days (DHCA), 19.89±13.8 days (ACP) and 17.87±10.85 days (RCP).

Figure 15. Duration of post-operative care

DHCA, deep hypothermic circulatory arrest; ACP antegrade cerebral perfusion; RCP, retrograde cerebral perfusion. Mean values of patients surviving the intensive care stay (23, 57 and 14 patients) and hospital stay (19, 51 and 13 patients), DHCA, ACP and RCP respectively, are represented

3.6   Mortality

Overall mortality was not influenced by the type of cerebral protection applied. The first 48 post-operative hours are characterized by the highest mortality rates and thus remain the critica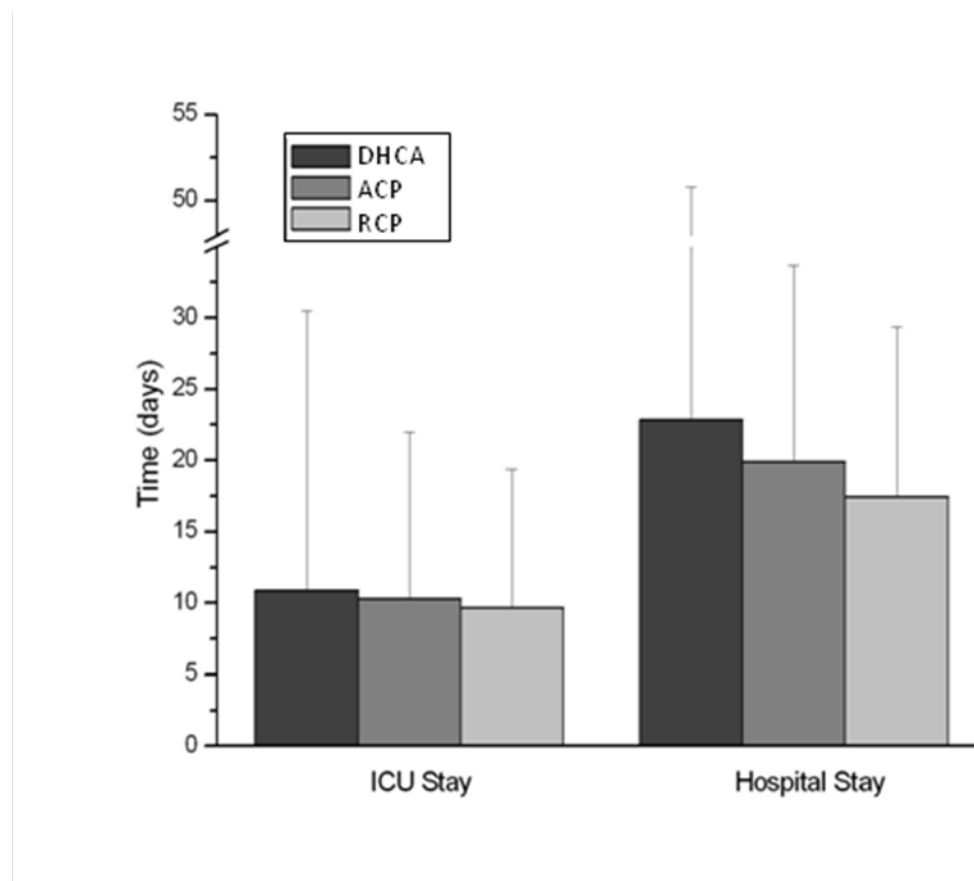l time-frame in all the subgroups (Table 11). Performance of additional surgery similarly increased mortality in all groups, however without reaching the level of significance, probably because of the small sample sizes (Table 12).

Table 11. Overall mortality

	DHCA		ACP		RCP		P	1-β
Nr. of Patients	**37**	**%**	**70**	**%**	**21**	**%**	**-**	**%**
ONLY AORTA	**6/22**	**27.3**	**8/37**	**21.6**	**2/7**	**28.6**	**0.768**	**9**
Intra-OP	0/22	0.0	3/37	8.1	0/7	0.0	0.679	20.1
48 h post-OP	4/22	18.2	3/34	8.8	1/7	14.3	0.476	21.3
30 days post-OP	2/18	11.1	2/31	6.5	1/6	16.6	0.508	8.4
In-Hospital	0/16	0.0	0/29	0.0	0/5	0.0	1.0	-
AORTA with add OP	**6/15**	**40.0**	**11/33**	**33.3**	**7/14**	**50.0**	**0.520**	**10.8**
Intra-OP	1/15	6.7	1/33	3.1	2/14	14.3	0.327	9.7
48 h post-OP	2/14	14.3	6/32	18.8	5/12	41.6	0.240	20.6
30 days post-OP	1/12	8.3	3/26	11.5	0/7	0.0	0.736	8.4
In-Hospital	1/11	9.1	1/23	4.3	0/7	0.0	0.675	12.3

Whereas additional cardiac or aortic root surgery did not worsen post-operative survival, the extension of the aortic replacement influenced mortality. Hemiarch replacement was associated with lower mortality risk than total arch replacement (Table 12). Furthermore, the recent use of the Evita prosthesis seems to reduce the mortality in the entire arch replacement ACP subgroups, however without reaching the level of significance because of the low sample size.

Table 12. Influence of type of operation on 30 days mortality

	DHCA		ACP		RCP		P	1-β
Total Patient Nr.	**37**	**%**	**70**	**%**	**21**	**%**	**-**	**%**
ONLY AORTA	**6/22**	**27.3**	**8/37**	**21.6**	**2/7**	**28.6**		
Hemiarch Replacement	2/5	40.0	2/5	40.0	0/0	0.0	1.0	-
Total Arch Rep / FET	4/17	23.5	5/24	20.8	2/7	28.6	0.444	20.7
Evita-Open	0/0	0.0	1/8	12.5	0/0	0.0	1.0	-
AORTA with add OP	**6/15**	**40.0**	**11/33**	**33.3**	**7/14**	**50.0**		
Hemiarch Replacement	2/8	25	2/12	16.7	1/1	100.0	**0.321**	**7.2**
Total Arch Rep / FET	3/7	42.9	9/18	50.0	6/13	46.2	**0.912**	**4.2**
Evita-Open	0/0	0.0	0/3	0.0	0/0	0.0	1.0	-

3.7 Relationship between Visceral Dysfunction and Mortality

Further statistical analysis revealed that independently of the type of cerebral protection used, early increase in the GPT ($P<0.05$) is associated with mortality, whereas GGT remains similarly low in all patients during the first 5 post-operative days (Figure 16). Similarly, both bilirubin and AP remain initially unchanged and begin to increase only after the first week of the post-operative period. Therefore these markers are rather useful in predicting only later risk for mortality (Figure 17).

Figure 16. Hepatic function and mortality
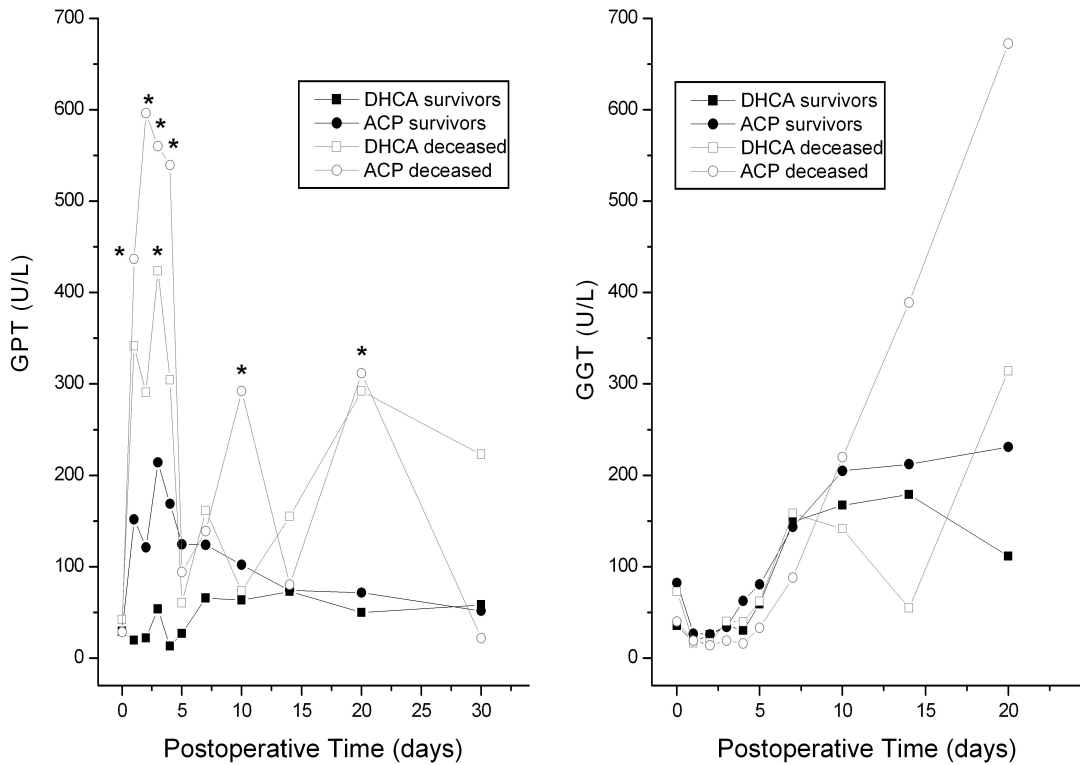
Figure 17. Gastrointestinal inflammation and mortality
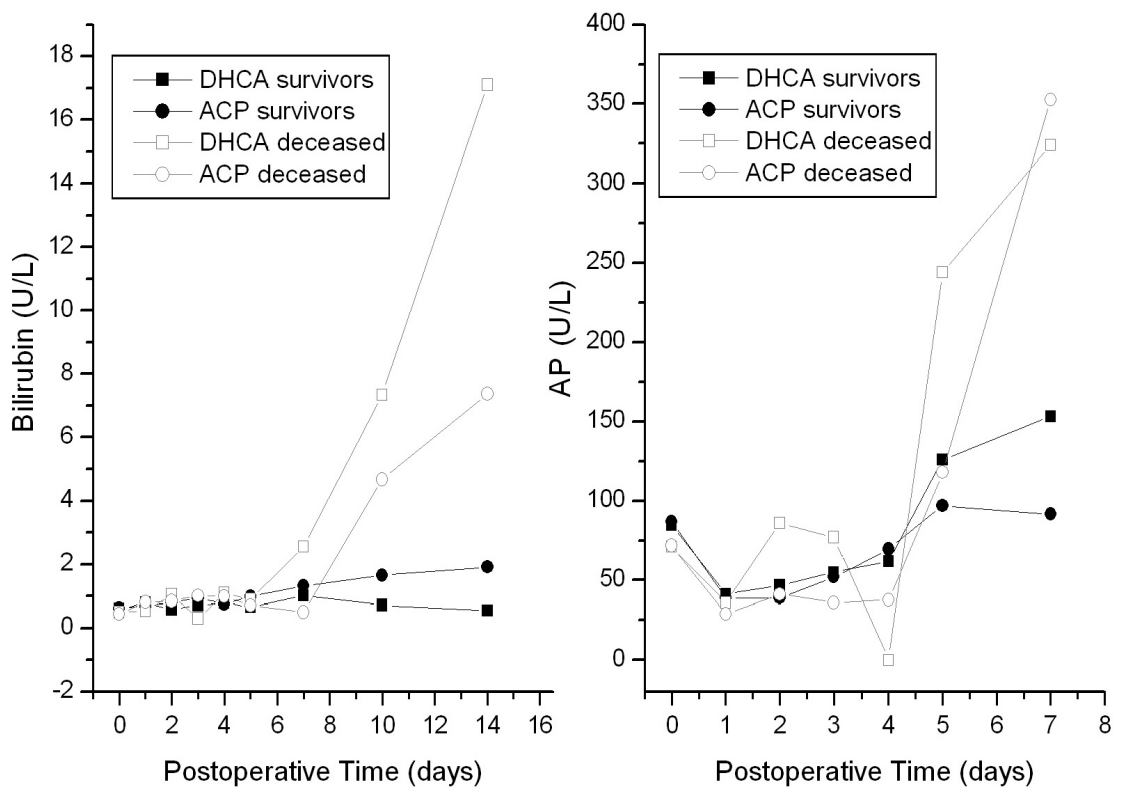
Mean values of laboratory parameters are represented. DHCA, deep hypothermic circulatory arrest survivors (n=25) and non-survivors (n=12); ACP, antegrade cerebral perfusion survivors (n=51) and non-survivors (n=19). *, P<0.05 deceased vs. survivors in the same cerebral protection group.

Figure 18. Intestinal ischemia/reperfusion damage and mortality
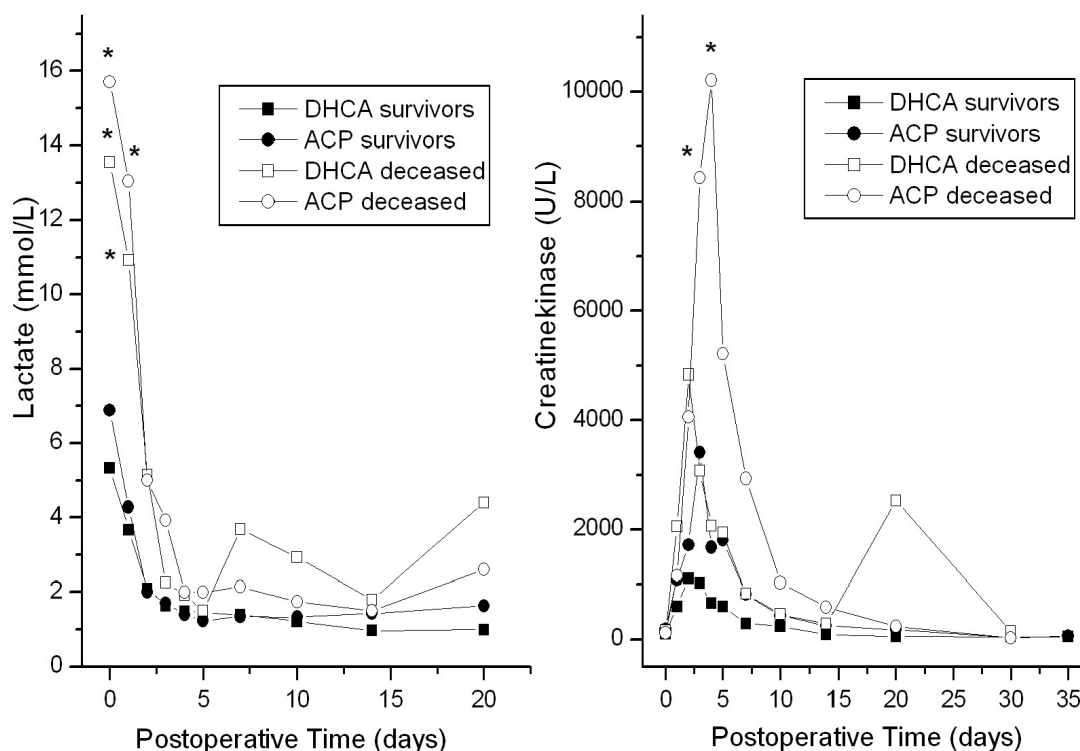
Figure 19. Renal function and mortality
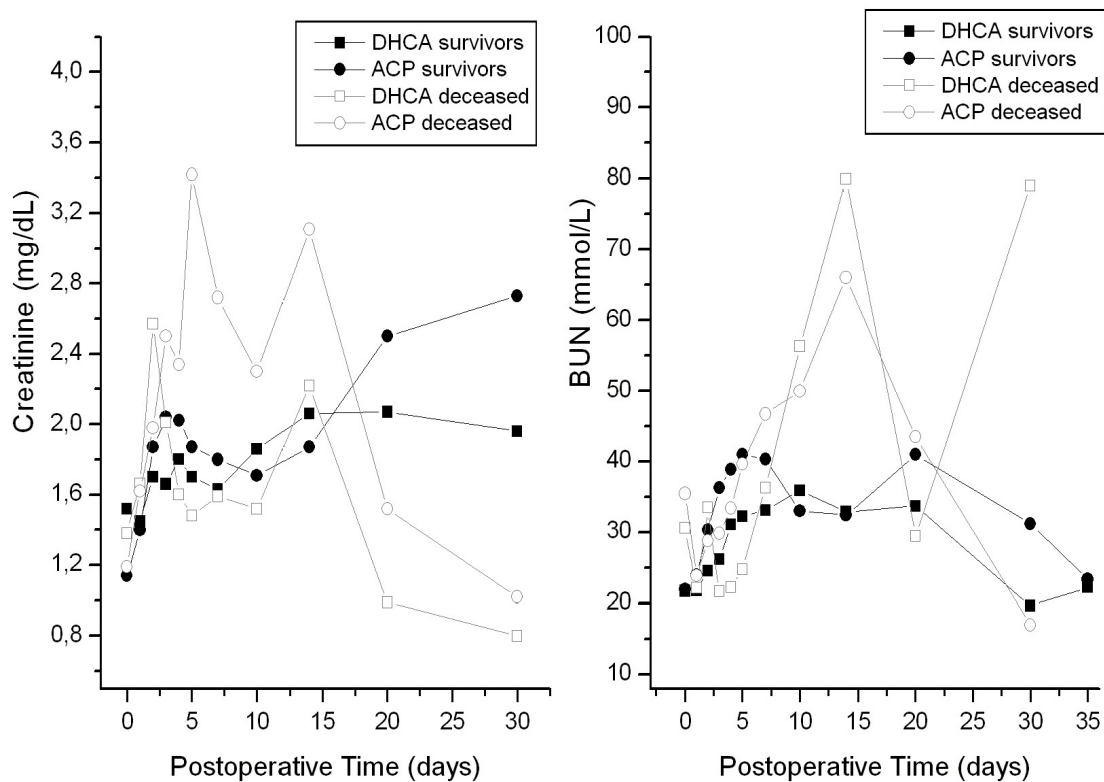
Mean values of laboratory parameters are represented. DHCA, deep hypothermic circulatory arrest survivors (n=25) and non-survivors (n=12); ACP, antegrade cerebral perfusion survivors (n=19) and non-survivors (n=51). *, P<0.05 deceased vs. survivors in the same cerebral protection group.

Lactate seems to be the most sensitive early marker of intestinal damage and mortality (P< 0.01) independently of the type of cerebral protection used. The early post-operative increase of the serum CK seems to be a relevant marker only for patients receiving antegrade cerebral perfusion (P< 0.05) and remained rather insensitive when circulatory arrest is solely used (Figure 18).

Markers of renal function (Figure 19) change without showing any trend and without reaching the level of significance.

The analysis of the pre-operative markers reveals that lactate - as marker of already pre-operatively present ischemia and hemodynamic instability- is a relevant predictor for early mortality in all groups independently of type of intra-operative perfusion used (Figure 20).

Figure 20. Relationship between pre-operative lactate values and mortality
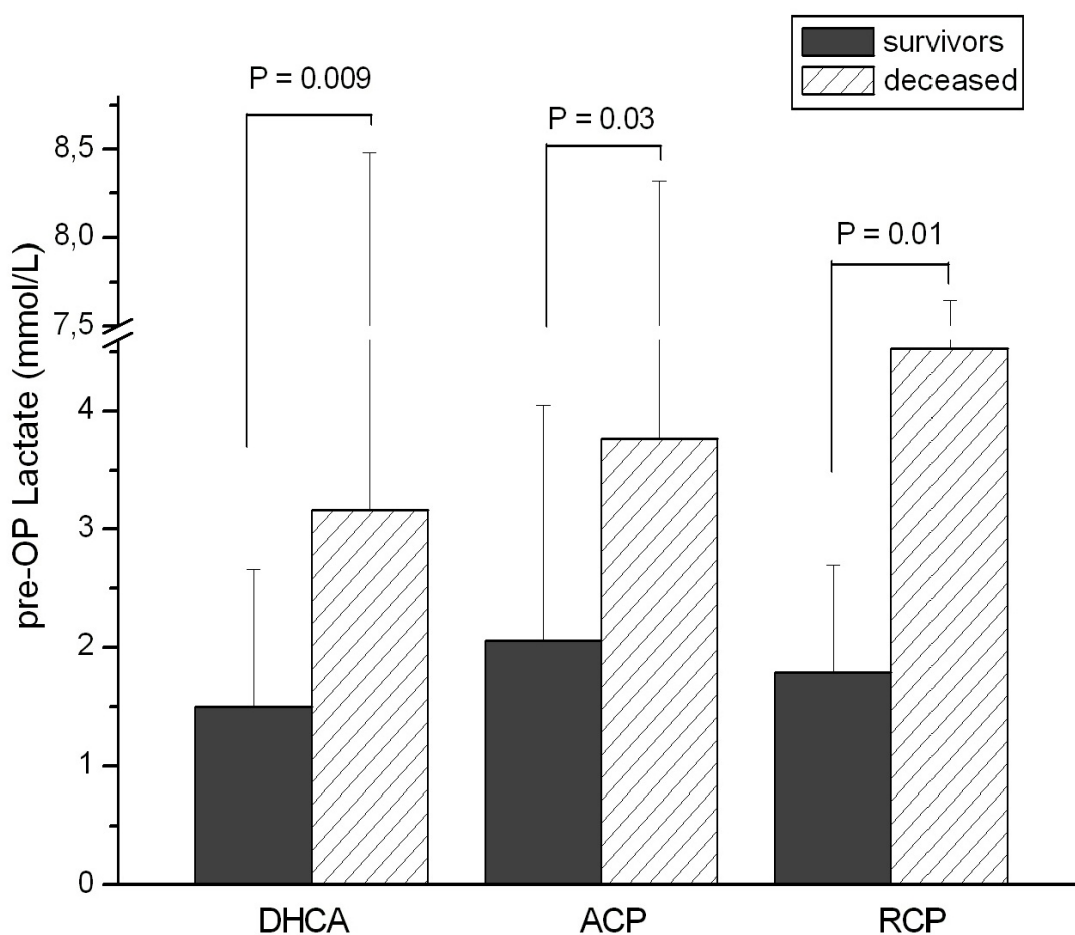
4   Discussion

Intra-operative splanchnic damage and intestinal barrier dysfunction are implicated as important triggering events in the development of post-operative multiorgan dysfunction. Transmural intestinal necrosis is the most deleterious form of intestinal damage and is related to significant mortality and morbidity mainly attributed to diagnostic delay (Acosta et al. 2006).

The early diagnosis of abdominal malperfusion remains difficult. To date, there is no systematic report on the incidence of non-occlusive splanchnic ischemia after aortic arch surgery, mainly due to the low rate of postmortem examinations and the cause of death stated as multi-organ failure.

To study visceral damage during aortic surgery with circulatory arrest, we analyzed conventional markers of hepatic, intestinal and renal damage in patients undergoing different cerebral protection techniques.

In this study, the three different protection and perfusion strategies used during surgical repair of the diseased aortic arch were associated with comparable survival at discharge (Table 11). Furthermore, no significant difference was found in the incidence of adverse operative outcome (Table 5, Table 9, Table 10). Thus, all three approaches could remain viable tools in similar patient populations.

The rates of early reoperation in our study (Table 5) were similar between the groups and are comparable to those reported in the contemporary era (Estrera et al. 2008; Milewski et al. 2010; Halkos et al. 2009) despite a high frequency of acute type A dissection (>71%, Table 3) and total arch repair (>64%, Table 4) in our cohort. This could be explained by the similar extent of aortic repair (Table 4), which led to similar mean operative, ischemic, arrest and reperfusion times (Table 5). Moreover, the need for additional surgical procedures may have prolonged the cardiac arrest time and total operation time, however without influencing the circulatory arrest times (Figure 1).

Although variable additional surgeries have been necessary, the incidence of additional surgical procedures assessed in each subgroup was comparable between the groups (Table 4), allowing an objective comparative evaluation of visceral function based on the adjacent perfusion technique.

Previous studies (Kawahito et al. 2003) showed that patients with acute coronary involvement during type A aortic dissection often underwent additional CABG procedure which was associated with a high risk of post-operative low cardiac output syndrome and in-hospital death. The present results cannot bring any new insights in this issue: although an assessment of the impact of additional CABG on post-operative cardiac function and visceral dysfunction was beyond the scope of the study, CABG resulted in comparable cardiac function during the post-operative period (Figure 7).

Nonetheless, whereas a lower proportion of patients required intra-operative catecholamine administration in the RCP group (Figure 2), a higher proportion of the patient receiving ACP or RCP required blood products (Figure 3). However, the amounts of catecholamine and blood products administered intra-operatively were similar in the three main groups (Figure 3, Figure 5) suggesting no superiority of one or another cerebral protection technique in terms of systemic homeostasis at the end of the operation (Table 6, Table 8). Similar requirements for buffer administration (Figure 2, Figure 3) might suggest that a correct hemodynamic and homeostatic equilibrium has been achieved in all patients.

Patient status at presentation represents an important predictive factor for the post-operative outcome and the pre-operative presence of mesenteric malperfusion is considered the most devastating condition (Totsugawa et al. 2010). Even more, Pacini et al. (2013) affirm that malperfusion of more organ systems before the operation makes immediate proximal aortic repair sub-optimal and the prognosis really unfavorable. Other studies (Wurm et al. 2017; Pang et al. 2012) revealed that lactate and base deficit at admission were associated with post-operative non-occlusive mesenteric ischemia after cardiac procedure under CPB without circulatory arrest. Takasu et al. (2007) demonstrated that base deficit at admission was associated with the duration of pre-operative cardiac resuscitation in hemodynamically instable patients, but not with mortality. In the present study, no significant differences in terms of blood gas analysis were assessed between the groups at the time of admission (Table 7), and this finding corresponds to the high percentage of hemodynamically stable patients identified in each group before the operation (Table 2), without any signs of intestinal ischemia.

Based on the results of Wurm et al. (2017), also seems that avoidance of hypoxia during the intensive care stay, that also characterizes the present findings, may prevent worst outcome of pre-existing non-occlusive mesenteric ischemia. The present study reveals that the first post-operative blood gas analysis (Table 8) showed similar values in the three main groups, reflecting a similar pharmacological and anesthesiological support during the operation.

However, coagulation disorders at operation could be accentuated by longer CPB times (Hong et al. 2017). In this respect, the present findings unveiled no significant differences in the subgroups with and without additional surgical procedures during the post-operative period (Figure 9, Figure 10). These findings might support the importance of inflammatory and oxidative mechanisms in the development of post-operative complications after complex aortic surgery and less importance of the surgical trauma and CPB-associated hemolysis per se.

Similar continuation therapy during the intensive care stay is reflected by the findings presented in Table 9, Table 10 and Figure 7. No differences in terms of duration of ventilation, renal replacement therapy, catecholamine substitution and antibiotic therapy were found between the groups. However, an important finding of the present study is that cerebral perfusion during circulatory arrest - either antegrade or retrograde - was associated with a significant reduction in the catecholamine index during the post-operative period (Figure 8). This finding corresponds to the previous results of Algra et al. (2012a) who revealed lower catecholamine index values in newborn and pediatric patients receiving antegrade cerebral perfusion during aortic arch replacement.

In terms of pharmacological support with blood products and coagulation factors no significant differences between the groups have been observed during the intensive care stay (Figure 10, Figure 11). In this respect, Wurm et al. (2017) previously reported successful conservative treatment with erythrocyte concentrates and antibiotics for intestinal bleeding. The protective effect of supportive antibiotic treatment in the early stage of non-occlusive mesenteric ischemia was also suggested by Tendler (2003). It cannot be excluded that a similar mechanism could have offered a certain protection in our study as well.

Although blood gas analysis emphasized good homeostasis achieved at the discharge from operation theatre in all groups (Table 8), lactate values were significantly increased when other surgical procedures were additionally performed to the frozen elephant trunk or when RCP was used (Figure 9). All together, these findings might suggest that hemodynamic instability and the subsequent intensity of ischemia-reperfusion damage remain important causes of post-operative visceral dysfunction. However, Wurm et al. (2017) failed to observe a direct association between the duration of cardiopulmonary bypass and the occurrence of non-occlusive mesenteric ischemia.

Whereas contradictory results have been presented with respect to the impact of the length of cardiopulmonary bypass time on the mesenteric circulation, we agree with the idea that

short times of hemodynamic instability are more relevant that the length of periods of stable mechanical support in influencing visceral function.

Experimental studies demonstrated that endothelial dysfunction is responsible for the post-operative intestinal malperfusion (Andrási et al. 2002; Andrási et al. 2003; Andrási et al. 2005). In the presence of pre-operative chronic low-cardiac output, smooth muscle cell injury additionally occurs in the mesentery after CPB. Accordingly, different vasoconstricting drugs given during resuscitation can influence systemic and mesenteric perfusion and oxygenation during the post-resuscitation period. Studer et al. (2002) assessed higher right atrial hemoglobin oxygen saturation and lower intestinal tonometric pCO_2 and lactate levels after vasoconstrictor administration, and both lactate and creatine kinase demonstrated to be reliable early markers of mesenteric ischemia and reperfusion injury in an experimental setting (van der Voort et al. 2014). On the other side, therapeutic hypothermia increases the resistance of the intestine to ischemia-reperfusion injury (Albrecht et al. 2012).

Taken together, the occurrence of visceral injury seems to be multifactorial and is mostly influenced by a combination of acute ischemic injury during circulatory arrest in mild-to-moderate hypothermia, as well as pre- and post-operative hemodynamic fluctuations after dissection and extensive occlusion of the collateral pathways.

The present study reveals that markers of visceral function changed differently during the post-operative period. Whereas GPT increased during the first 5 to 10 post-operative days in the ACP and RCP groups, GGT remained unchanged at the beginning and increased in all groups after the 5th post-operative days remaining higher up to the 30th post-operative day (Figure 11). The markers of gastrointestinal inflammation (Figure 12) showed fewer changes during the 30 post-operative days than the hepatic markers, supporting a possible anti-inflammatory effect of the systemic deep hypothermia (Albrecht et al. 2012).

Leukocyte count remains an unspecific parameter for non-occlusive mesenteric ischemia. Previous studies (Schuetz et al. 2010) showed that leukocytes were similarly elevated for as long as seven days, in patients subjected to operations with cardiac arrest independently from the presence of infections.

Oppositely, from the two markers of intestinal ischemia/reperfusion injury presented in Figure 13, lactate showed high levels already before the operation and decreases abruptly after the aortic repair, whereas creatine kinase started to increase after the operation and continued to increase during the first 48 post-operative hours in all groups. These findings clearly demonstrate that the early ischemia/reperfusion injury during the surgical procedure

causes an early intestinal damage that could generate remote effects and thus influence the function of the other abdominal organs.

Several possible mechanisms were shown to be responsible for the mesenteric ischemia after circulatory arrest. First, mesenteric injury caused pre-operatively by dissection and subsequent malperfusion can be easily exacerbated by reperfusion after aortic surgical repair under circulatory arrest, resulting in coagulopathy, organ dysfunction, and systemic metabolic abnormalities (Fernandes et al. 2012; Fernández Suárez et al. 2017). However, the present study revealed similar degree of abdominal aortic involvement in all groups.

Second, although epinephrine may induce more myocardial damage related to its beta-adrenergic inotropic action and may increase the severity of postresuscitation myocardial dysfunction (Tang et al. 1995), the use of epinephrine in the present cohort is compliant with the results of previous studies demonstrating that epinephrine for resuscitation tends to be associated with higher resuscitation rates (Studer et al. 2002) and improved intestinal perfusion. On the other hand administration of vasopressin was shown to result in higher cardiac output, less regional mesenteric ischemia (by pCO_2 gap) and lower lactate levels. In contrast, Prengel et al. (1998) demonstrated an increased cardiac depressant effect of vasopressin compared with epinephrine. These conflicting effects of vasopressin seem to be explained by the biphasic effect (initial strong vasoconstriction followed by vasodilatation) assessed on isolated human mesenteric arteries (Martinez et al. 1994). Moreover, vasopressin-induced mesenteric vasoconstriction (Iwao et al. 1996) might be accentuated by the increased levels of endogenous angiotensin during resuscitation (Reilly et al. 1992; Reilly and Bulkley 1993).

Third, intestinal ischemic injury leads to disruption of the gut mucosal barrier and prompt release of endotoxin into the portal circulation; subsequently, hepatic macrophages produce tumor necrosis factor, which is an important mediator of reperfusion injury (Caty et al. 1990). This mechanism explains the present findings revealing initial intestinal damage followed by later hepatic dysfunction. Hepatic dysfunction has been described also after cardiac arrest without circulatory arrest (Cerchiari et al. 1993) and was also shown to be associated with bacteriemia in the visceral post-resuscitation syndrome.

As the present results reveal, independently from the type of cerebral protection used, the mesenteric ischemia/reperfusion injury is the early phenomena that may be documented after the procedure. Oppositely, the abdominal markers of bowel inflammation, hepatic injury and kidney dysfunction remain unchanged up to the 5th post-operative day in all

groups. Moreover, the markers of kidney function (Figure 14, Figure 19) remain difficult to be interpreted because of the effect of renal replacement therapy.

Forth, a recent experimental study in a rat model (Karhausen et al. 2013) revealed that primary injury caused by deep hypothermic circulatory arrest in the intestine is an ischemia/reperfusion type injury and revealed for the first time the role of mast cells in the gut injury and systemic inflammatory responses. They emphasize that mast cells translate splanchnic microvascular hypoperfusion into an immune-inflammatory responses following cardiac surgery. Intestinal ischemia/reperfusion injury was also shown to be a primary event following rewarming after DHCA (Karhausen et al. 2013) and playing an important role in both, local and systemic inflammation.

Apart from these four pathological mechanisms, therapeutic hypothermia was shown to increase the resistance of the intestine to ischemia-reperfusion injury (Albrecht et al. 2012). Moreover, it seems that in hemodynamically stable patients, hypothermia remains the major protective tool of visceral organs also during circulatory arrest. In the adults, collateral perfusion offered by ACP did not significantly protect against post-operative visceral dysfunction. Previous studies have demonstrated that in neonates with congenital heart failure undergoing complex aortic arch repair (Algra et al. 2012a; Algra et al. 2012b), abdominal organs are better protected by low-flow ACP than by DHCA. These studies also indicated that increased DHCA duration adversely affects post-operative recovery, whereas even prolonged ACP is apparently without consequences (Algra et al. 2012a). However, in the case of aortic dissection – which is characteristic to the present adult cohort – no significant difference in the visceral function was assessed between the groups undergoing different type of cerebral protection.

Consistent with the similar modifications of visceral function in the present study, mortality did not differ significantly between the groups; although mortality tended to be higher in patients receiving additional operation or total arch replacement, this did not achieve the level of significance, probably due to the relatively small patient numbers documented in each subgroup (Table 11, Table 12).

Based on the present findings, we incline to believe that the pre-operative hemodynamic instability is playing a decisive role in the post-operative outcome.

Wurm and Zierer (Wurm et al. 2017; Zierer et al. 2007) found that patients who died of non-occlusive mesenteric after cardiac arrest had elevated lactate and greater base excess at admission than the survivors. Similarly, van Arsdell et al. (1998) noted in an autopsy series of acute type A aortic dissection that unoperated patients often had only one entry and

reentry tear compared with patients operated on with aortic cross-clamping, who generally had multiple tears. Indeed, changes in the hepatic markers (Figure 16) and markers of intestinal inflammation (Figure 17) occurred at similar time-points in all patients in the present study, and these changes were more accentuated in the non-surviving patients than in survivors. In particular, the markers of intestinal ischemia/reperfusion injury showed significantly higher levels in the deceased patient group that in the survival group (Figure 18).

Moreover, the data of the present study confirm that pre-operative lactate values were significantly increase in each group of non-survivals (Figure 29), and the different types of cerebral protection methods that have been applied could not reduce the impact of pre-operative status on mortality.

Therefore patient status at presentation represents an important predictive factor for post-operative outcome in patients receiving aortic arch replacement.

4.1 Limitations

Limitations of this study are due to the retrospective design and the heterogeneity of the cohort as well as to the small number of patients in the subgroup.

While some parameters were confirmed to be associated with visceral ischemia, caution should be applied when interpreting these results because of the small number of cases. The incidence rates might not be the same in other populations.

The markers of hepatic dysfunction (GPT, GGT), intestinal inflammation (Bilirubin, AP) and renal injury (Creatinine, BUN) were not significantly influence by the type of cerebral protection used. Although lactate and CK were the only markers associated with mortality in the present study, they are not solely associated with gastrointestinal dysfunction; therefore a cause-effect relationship between visceral injury and mortality after open surgical aortic arch replacement cannot be proven.

Since the cause of death was most often stated as apparent and part of post-dissection or post-circulatory arrest multi-organ failure, post-mortem exams were not routinely performed in this cohort; that limited the possibility of identifying the cases of non-occlusive mesenteric ischemia based on the pathological report.

4.2 Conclusion

1. ACP and RCP offer no significant protection of abdominal viscera during circulatory arrest. Their principal benefit remains cerebral protection.

2. The parameters determined in the present study were in normal range in the early post-operative period in all groups. Differences occurred in the later post-operative period emphasizing that hypothermia offers similar visceral protection independently from the type of cerebral perfusion used. The later differences in biomarkers could be associated with the degree of true lumen opening and the subsequent degree of visceral perfusion.

3. GPT, Lactate and Creatine kinase seem to be sensitive markers of early visceral damage, whereas GGT, Bilirubin and AP were markers of delayed visceral dysfunction. Creatinine and BUN can be hardly interpreted because of the interference with renal replacement therapy during the early post-operative period.

4. Early increase in plasma lactate and CK are associated with increased mortality.

5   Summary

The purpose of the current investigation was to determine how different approaches of cerebral protection (DHCA, ACP and RCP) influence abdominal organ function after open surgical aortic arch replacement and establish relationships to operative mortality, clinical outcome, and long-term survival.

Demographic data, pre-operative and operative characteristics as well as post-operative markers of visceral function were retrospectively analyzed in 128 patients with acquired aortic arch disease who underwent open surgical aortic arch replacement under DHCA, ACP or RCP between June 2005 and March 2016 at the Department of Thoracic, Cardiac and Vascular Surgery, University of Göttingen, Germany.

There were no significant differences between the three groups of patients in terms of demographic data, clinical status, disease extension, characteristics of the surgical techniques, operative times and need for revision. However, DHCA patients required significantly more catecholamine support during the post-operative period than ACP or RCP patients.

GPT, Lactate and Creatine kinase seem to be sensitive markers of early post-operative visceral damage whereas GGT, Bilirubin and AP are markers of delayed visceral dysfunction. Higher pre-operative lactate levels, as well as early post-operative increase in plasma lactate and CK were associated with mortality in all groups independently of type of intra-operative perfusion used.

Therefore, ACP and RCP offer no significant protection of abdominal viscera during circulatory arrest. Their main advantage seems to remain in the field of cerebral protection. The main protector of visceral organs seems to be deep hypothermia that was similarly applied in all three groups.

6 Zusammenfassung - Summary in German

Zielsetzung der vorliegenden Arbeit war es zu bestimmen, inwieweit die verschiedenen Vorgehensweisen für die zerebrale Protektion (Kreislaufstillstand mit tiefer Hypothermie (DHCA), antegrade zerebrale Perfusion (ACP) und retrograde zerebrale Perfusion (RCP)) bei offen-chirurgischem Aortabogenersatz die Funktion der abdominalen Organe beeinflussen. Weiterhin sollten auf Basis geeigneter Parameter Beziehungen zu operativer Mortalität, klinischem Ergebnis und Langzeit-Resultaten etabliert werden.

Demographische Daten, prä-, intra- und post-operative Charakteristika sowie post-operative Marker der viszeralen Funktion wurden in einer retrospektiven Studie analysiert. Basis der Untersuchung waren 128 Patienten mit erworbener Erkrankung des Aortabogens, die sich im Zeitraum zwischen Juni 2005 und März 2016 einem offen-chirurgischen Aortabogenersatz unter Zuhilfenahme der zerebralen Protektionstechniken DHCA, ACP, RCP in der Klinik für Thorax-, Herz- und Gefäßchirurgie der Universität Göttingen, Deutschland, unterzogen haben.

Bezüglich der Parameter demographische Daten, klinischer Status, Ausdehnung der Erkrankung, Charakteristika der chirurgischen Techniken, OP-Zeiten und Notwendigkeit von Revisionen wiesen die drei untersuchten Gruppen keine signifikanten Unterschiede auf. Jedoch benötigten die Patienten der DHCA-Gruppe signifikant höhere Gaben an Katecholaminen während der post-operativen Phase als die Patienten der ACP- oder RCP-Gruppen.

Glutamat-Pyruvat-Transaminase, Laktate und Creatine kinase scheinen sensitive Marker für eine frühe post-operative viszerale Schädigung darzustellen, während Gamma-Glutamyl-Transpeptidase, Bilirubin und AP Marker einer verzögerten viszeralen Dysfunktion sind. Erhöhte präoperative Laktatwerte sowie ein früher post-operativer Anstieg der Plasma-Laktate und der Creatine kinase stehen in Verbindung mit Mortalität in allen Gruppen, unabhängig vom Typ der intra-operativ angewandten Perfusionsverfahren.

Deshalb bieten ACP und RCP keinen signifikant erhöhten Schutz der abdominalen viszeralen Organe während eines Kreislaufstillstands. Ihr Hauptvorteil scheint auf dem Bereich des zerebralen Schutzes zu liegen. Der bedeutendste Protektionsfaktor der viszeralen Organe bleibt wohl nach wie vor die tiefe Hypothermie, die in allen drei Gruppen in ähnlicher Weise zur Anwendung kam.

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