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Abdominal Organ Dysfunction after Open Aortic Arch Surgery using Different Cerebral Protection Strategies

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Abstract

Background: A positive impact of Antegrade Cerebral Perfusion (ACP) on neurological function and survival in patients undergoing open aortic arch surgery under Deep Hypothermic Circulatory Arrest (DHCA) has been emphasized but the suggested secondary remote protective effects of ACP on the abdominal organ function through collateral perfusion remains controversial.

Methods: Markers of visceral function were retrospectively analyzed in adults with acquired aortic arch disease who underwent DHCA (n=37) or ACP (70) for open surgical aortic arch replacement at one institution.

Results: Preoperative characteristics (ascending aortic dissection: 78.4% *vs.* 71.4%, p=0.436; abdominal extension: 29.1% *vs.* 31.4%, p=0.857; hemodynamic instability: 8.1% *vs.* 10.0%, p=0.749), intraoperative data and complications were similar. Preoperative lactate, postoperative inotropic support and maximal postoperative ALT, CK and lactate levels were significantly higher in non-survivors vs. survivors (p<0.05) in both ACP and DHCA groups.

Maximal postoperative CK and lactate correlated with the preoperative lactate values (p<0.05 and p<0.01) whereas ALT and lactate correlated with postoperative inotropic index (p<0.05, p<0.0001) in both groups. Although maximal postoperative ALT and CK differed in the univariate analysis (p<0.05), they failed to demonstrate an independent predictor capacity for death.

Multivariate analysis revealed an association between mortality and preoperative hemodynamic instability (HR=3.69, p=0.023), maximal postoperative lactate (HR=1.02, p=0.0001) and maximal postoperative inotropic score (HR=1.00, p=0.006).

Conclusion: ACP did not influence postoperative abdominal biomarkers; thus, a direct protective effect through improved arterial collateral circulation remains implausible. Hemodynamic instability and cardio-circulatory failure rather than visceral dysfunction seem responsible for mortality after open surgical aortic arch replacement.

Keywords: Deep hypothermic circulatory arrest; Antegrade cerebral perfusion; Visceral malperfusion; Abdominal biomarkers

Abbreviations

ACP: Antegrade Cerebral Perfusion; AP: Alkaline Phosphatase; AUC: Area under the Curve; BUN: Blood Urea Nitrogen; CPB: Cardiopulmonary Bypass; CK: Creatin Kinase; DHCA: Deep Hypothermic Circulatory Arrest; ALT: Alanine Amino Transferase; GGT: γ-Glutamyl Transpeptidase; HR: Hazard Ratio; ICU: Intensive Care Unit; WBC: White Blood Cells

Introduction

Multi organ failure after open surgical aortic arch replacement occurs due to physiologic injuries initiated by aortic dissection, resuscitation, surgical treatment and postoperative pharmacological management [1-3]. Although the susceptibility of the intestine to microcirculatory hypoperfusion in the context of cardiac surgery is well-known [4,5], therapeutic hypothermia increases the resistance of the intestine to ischemia-reperfusion injury [6]. Antegrade Cerebral Perfusion (ACP) was suggested to provide more abdominal perfusion then does Deep Hypothermic Circulatory Arrest (DHCA) via the collateral circulation granted by the perfusion of the left subclavian arteries and this

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Table 1: Preoperative Demographic and Clinical Data in patients receiving aortic arch replacement.

Pat. Nr.	DHCA 37	ACP 70	P value
Age, Mean ± SD, (IQR)	63.6 ± 11.9 (55-75)	61.3 ± 11.4 (51-70)	0.33
BMI, Mean ± SD, (IQR)	28.3 ± 4.4 (25.0-31.2)	27.1 ± 4.4 (24.1-29.4)	0.183
Male Gender (%)	25 (67.6) (0.51-0.80)	44 (62.9) (0.51-0.73)	0.675
Art. Hypertension (%)	31 (83.8) (0.69-0.92)	61 (87.1) (0.77-0.93)	0.771
Smoking (%)	6 (16.2) (0.08-0.31)	12 (17.1) (0.10-0.28)	1
Diabetes mellitus (%)	5 (13.5) (0.06-0.28)	9 (12.9) (0.07-0.22)	0.931
Renal Disease (%)	8 (21.6) (0.11-0.37)	17 (24.3) (0.16-0.36)	0.755
COPD (%)	3 (8.1) (0.03-0.21)	5 (7.1) (0.03-0.16)	0.852
LV-EF, Mean ± SD of %, (IQR)	54.7 ± 11.9 (50-60)	51.9 ± 9.5 (45-60)	0.188
Hemodyn. Instable (%)	3 (8.1) (0.03-0.21)	7(10.0) (0.05-0.19)	0.749
Log. Euroscore, Mean ± SD	21.9 ± 13.7 (12.8-30.4)	25.5 ± 17.7 (12.2-36.8)	0.14
Disease Extension (%)			
Aortic Arch Aneurysm	7 (18.9) (0.09-0.34)	23 (32.9) (0.23-0.45)	0.127
Aortic Dissection			
Ascending Aorta	29 (78.4) (0.63-0.89)	50 (71.4) (0.59-0.81)	0.436
Aortic Arch	31 (83.8) (0.69-0.92)	52 (74.3) (0.63-0.83)	0.265
Descending Aorta	18 (48.7) (0.33-0.64)	35 (50.0) (0.39-0.61)	0.898
Abdominal Extension	11 (29.7) (0.17-0.46)	22 (31.4) (0.22-0.43)	0.857
Disease Gravity (%)			
Pericardial Effusion	11 (29.7) (0.17-0.46)	19 (27.1) (0.18-0.39)	0.777
Intramural Hematoma	0 (0.0) (0-0.09)	7 (10.0) (0.05-0.19)	0.047
Contained Ao. Rupture	2 (5.4) (0.02-0.18)	8 (11.4) (0.06-0.21)	0.312
Free Aortic Rupture	0 (0.0) (0-0.09)	2 (2.9) (0.01-0.1)	0.298

Categorical variables are expressed as rates ± 95% CI and continuous variables as mean ± SD and IQR (25° to 75° percentile); DHCA, deep hypothermic circulatory arrest; ACP, antegrade cerebral perfusion; IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LV-EF, left ventricular ejection fraction; P<0.05 is statistically significant

likely has a protective effect on abdominal organs [7,8]. Therefore, the presence of abdominal malperfusion under hypothermia and circulatory arrest remains difficult to diagnose. The impact of cerebral protection [9,10] and abdominal organ dysfunction on the operative mortality after aortic arch replacement has been difficult to elucidate.

The purpose of the current investigation was to determine how different approaches of cerebral protection used for open surgical aortic arch replacement may influence visceral organ function and to establish possible relationships of visceral dysfunction to clinical outcome and mortality.

Methods

Study design and 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 University of Göttingen, Germany. Patients with congenital diseases or requiring repeated aortic arch replacement were excluded from the present study. DHCA was applied in 37 patients, whereas direct two-vessel (brachiocephalic trunk and left carotid artery) ACP in 70 patients. Twenty one patients receiving retrograde cerebral perfusion were not included in the present analysis.

The study was approved by the Ethics Committee of the University (reference: 2/10/17), and a waiver of consent was obtained because of the study`s retrospective design.

Definitions

Hemodynamic instability was defined as a state where the circulatory system is not able to provide adequate perfusion of the tissues and requires inotropic resuscitation to maintain mean arterial blood pressure above 65 mmHg [11]. The *multiple organ dysfunction syndromes* represents a potentially reversible physiologic derangement of homeostasis involving two or more organ systems not involved in the primary disorder but that requires mandatory intervention [12].

Data collection

Demographic and clinical data, postoperative treatment and outcome were collected from routine care hospital charts. Operative and intraoperative times were extracted from the perfusion charts. The circulatory arrest time in the ACP groups is considered equivalent to the antegrade cerebral perfusion time. Markers of hepatic function (Alanine Amino Transferase (ALT), γ-Glutamyl Transpeptidase (GGT), and Bilirubin), gastrointestinal inflammation (Bilirubin, Alkaline Phosphatase (AP) and White Blood Cells Count (WBCs)), intestinal ischemia-reperfusion injury (lactate and Creatin Kinase (CK)) and markers of renal injury (Creatinine and Blood Urea Nitrogen (BUN)) were extracted to assess the degree of *abdominal organ dysfunction.*

Measurements

Hemodynamic function was estimated by cardiac output and

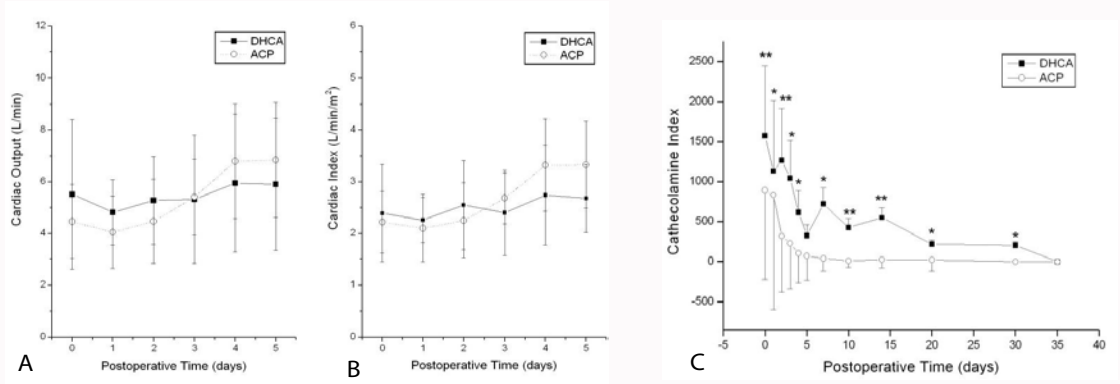

Figure 1: Postoperative time course of cardiac function and inotropic support in patients receiving aortic arch replacement. Cardiac index (1A), cardiac output (1B) and inotropic score (1C) in the DHCA and ACP groups at corresponding time points. While there was no difference in cardiac index and output, inotrope score was significantly increased in the DHCA-group.*, p<0.05, **, p<0.01, DHCA, deep hypothermic circulatory arrest; ACP, antegrade cerebral perfusion.

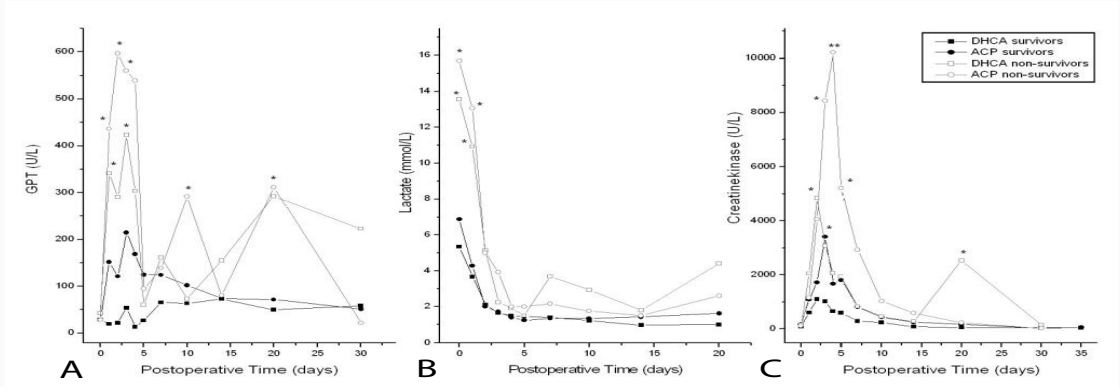

Figure 2: Early sensitive markers of abdominal organ function after aortic arch replacement. Mean values of ALT (2A), Lactate (2B) and CK (2C) in the DHCA and ACP groups at corresponding time points reveal significant increases in the non-survivors subgroups, independently of cerebral protection. *, p<0.05; **, p<0.01, DHCA, deep hypothermic circulatory arrest; ACP, antegrade cerebral perfusion.

index, as well as by the preoperative and postoperative lactate values. The inotrope score was calculated using the following formula (μg × kg^{-1} × min^{-1}): dopamine + dobutamine + (15 × milrinone) + (100 × epinephrine) + (100 × norepinephrine) [13]. The degree of inotropic support was estimated by the Area under the Curve (AUC) of the inotrope scores for each patient, calculated by linear function for ascending slopes and logarithmic function for the descending slopes.

Study outcome

The primary outcomes of the study were the abdominal organ dysfunction after aortic arch replacement and the end-point survival to hospital discharge. Abdominal organ dysfunction was regarded as the postoperative maximal value of the corresponding biochemical parameters (Figure 2) during the hospital stay and their relationship to the end-point survival at hospital discharge (post-hoc power of the study for lactate 100%, post-hoc power of the study for ALT 71.2%). Secondary outcomes included the impact of preoperative and intraoperative characteristics, and of postoperative treatment including postoperative inotrope scores, mechanical support and surgical reinterventions on abdominal organ function and mortality.

Statistical analysis

Results are expressed as mean ± SD and IQR (25° to 75° percentile) for continuous variables and as percentages ± 95% CI for categorical variables unless otherwise specified. Data comparisons were performed according to the type of cerebral protection tool using ANOVA followed by Student unpaired t test, x test or Fisher`s exact test as appropriate. The significant changes in continuous variables were assessed with a paired t test. The relationships between biomarkers were evaluated by simple linear regression. Slopes were compared in order to assess effects of the type of cerebral protection. The impact of independent predictors on survival was assessed with Cox proportional hazards models in univariate and multivariate analysis. Variables with a univariate value of P<0.05 were incorporated into the multivariate models. To avoid collinearity among a subset of several variables measuring the same phenomenon (e.g., peak inotropic score and AUC inotropic score), only the variable that had the strongest association with survival was entered into the multivariate models. Probabilities of event-free survival were obtained by Kaplan-Meier estimates for the 2 groups and then compared by a 2-sided log-rank test. P values <0.05 (2-sided) were considered as indicative of statistical significance. All statistical analyses were performed with Statistica (StatSoft Inc, Tulsa, OK, USA) and Origin Pro (Origin Lab, Northampton, Massachusetts, USA).

Results

Preoperative data

The epidemiological and clinical data were similar in the two groups (Table 1). Patients suffering from aortic aneurysms were operated electively whereas patients suffering from dissection were operated emergently. Similar neurological and ischemic baseline

Table 2: Surgical Data of patients receiving aortic arch replacement.

Pat. Nr.	DHCA 37	ACP 70	P value
Operative Times (min)			
Operation	425.9 ± 136.0 (335.5-467.5)	488.7 ± 175.3 (375-515)	0.061
CPB	295.5 ± 84.7 (240.5-333)	338.1 ± 126.1 (255-380)	0.068
Cooling	65.9 ± 21.5 (49-79)	74.0 ± 20.8 (60-90)	0.061
Cardiac Arrest	144.0 ± 37.1 (120.5-161.5)	164.0 ± 73.3 (110-211)	0.123
Circulatory Arrest	52.0 ± 20.8 (30-67.5)	68.5 ± 29.1 (51-84.5)	**0.003**
Rewarming	123.4 ± 34.4 (98-154.5)	122.8 ± 30.9 (100-150)	0.927
Lowest Temp. < 18°C (%)	32 (86.5) (0.72-0.94)	44 (62.9) (0.51-0.73)	**0.013**
Extent of Surgery (%)			
Hemi-arch Replacement	12 (32.4) (0.19-0.49)	18 (25.7) (0.17-0.37)	0.465
Total arch Replacement	25 (67.6) (0.49-0.78)	52 (74.3) (0.63-0.83)	0.465
Add. Aortic Root Surgery	11 (29.7) (0.17-0.46)	28 (40.0) (0.29-0.52)	0.295
Add. Cardiac Surgery	9 (24.3) (0.13-0.40)	15 (21.4) (0.13-0.32)	0.733
Surgical Reintervention (%)			
One Revision	14 (37.8) (0.24-0.54)	20 (28.6) (0.19-0.40)	0.333
Two Revisions	2 (5.4) (0.02-0.18)	3 (4.3) (0.01-0.12)	0.799
Three Revisions	0 (0.0) (0-0.09)	2 (2.9) (0.01-0.10)	0.298
Type of Reintervention (%)			
RS for thoracic bleeding	5 (13.5) (0.06-0.28)	7 (10.0) (0.05-0.19)	0.587
RS for acute cardiac failure	5 (13.5) (0.06-0.28)	2 (2.9) (0.01-0.1)	0.09
additional TEVAR	1 (2.7) (0.01-0.14)	2 (2.9) (0.01-0.1)	0.953
Vascular Access Revision	2 (5.4) (0.02-0.18)	2 (2.9) (0.01-0.1)	0.52
Hemicolectomy	0 (0.0) (0-0.09)	2 (2.9) (0.01-0.1)	0.298
Fasciotomy	0 (0.0) (0-0.09)	3 (4.3) (0.01-0.12)	0.203
Dialysis Catheter Impl.	1 (2.7) (0.01-0.14)	3 (4.3) (0.01-0.12)	0.68

Categorical variables are expressed as rates ± 95% CI and continuous variables as mean ± SD and IQR (25° to 75° percentile); DHCA: Deep Hypothermic Circulatory Arrest; ACP: Antegrade Cerebral Perfusion; IQR: Interquartile Range; CPB: Cardiopulmonary Bypass. P<0.05 is statistically significant

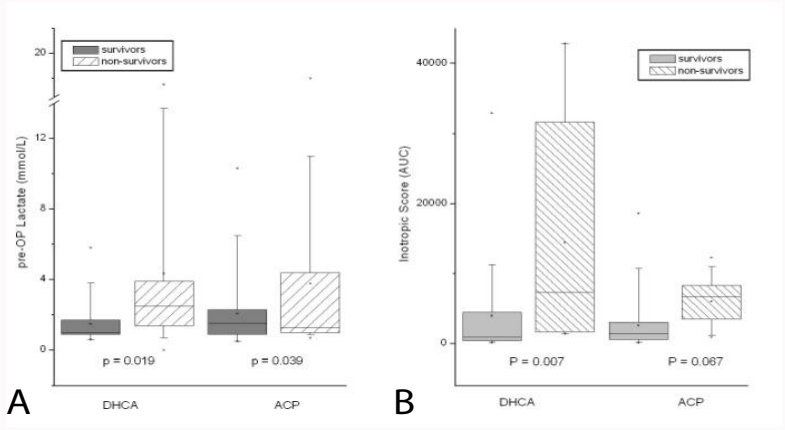

Figure 3: Preoperative lactate values and postoperative inotropic scores (AUC) after aortic arch replacement. Boxplot graphs illustrating the distribution of preoperative lactate values (3A) and area under the curve (AUC) of the postoperative inotropic support (3B) in patients treated with DHCA and ACP comparing survivors to non-survivors. Median values (bold line), interquartile range (box), and range (error bars) including outliners (crosses) are shown. DHCA, deep hypothermic circulatory arrest; ACP antegrade cerebral perfusion, p<0.05 is statistically significant.

characteristics were observed in both groups: 43.2% of the DHCA and 55.7% of the ACP patients suffered from thoracic pain at the time of admission (p=0.69), 10.8% and 15.7% respectively, suffered from cerebral neurological symptoms (p=0.57), 5.2% and 15.7% respectively suffered from lower limb neurological symptoms (p=0.21); whereas preoperative lower limb ischemia was documented in 2.7% of the DHCA patients and 5.7% of the ACP patients (p=0.66), none of the patients included in the DHCA group and 2 patients (2.8%) included in the ACP group suffered from abdominal pain before the operation (p=0.54). Baseline preoperative levels of the biochemical parameters

Table 3: Postoperative ICU Treatment and Outcome after aortic arch replacement.

Pat. Nr.	DHCA 37	ACP 70	P value
Postoperative Times (days)			
Ventilation	6.1 ± 12.7 (1-5)	5.4 ± 8.5 (1-5)	0.735
ICU Stay	12.9 ± 22.3 (3-11)	11.9 ± 11.5 (2-12)	0.76
Hospital Stay	29.3 ± 30.6 (15.5-28.5)	22.4 ± 14.2 (14.5-31)	0.114
ICU Treatment			
Catecholamine (%)	35 (94.6) (0.82-0.99)	67 (95.7) (0.88-0.99)	0.959
Catecholamine (days)	6.2 ± 8.4 (2-6.5)	4.4 ± 3.9 (2-5)	0.307
Transfusion – RBC (%)	25 (67.6) (0.51-0.80)	43 (61.4) (0.49-0.72)	0.408
Transfusion – FFP (%)	12 (32.4) (0.19-0.49)	18 (25.7) (0.17-0.37)	0.333
Transfusion – PC (%)	10 (27.0) (0.15-0.43)	25 (35.7) (0.26-0.47)	0.394
RBC (Units)	7.8 ± 10.2 (2-8)	8.3 ± 7.2 (3-10.5)	0.411
FFP (Units)	14.3 ± 20.1 (3-9)	7.4 ± 5.6 (4-14)	0.112
PC (Units)	4.1 ± 4.3 (2-4)	2.9 ± 1.1 (2-4)	0.076
Buffer (%)	27 (72.9) (0.57-0.85)	53 (75.7) (0.65-0.84)	0.738
Buffer (days)	2.3 ± 1.0 (2-2)	2.1 ± 0.6 (2-2)	0.199
Antibiotics (%)	36 (97.3) (0.86-0.99)	69 (98.6) (0.92-0.99)	0.52
Antibiotics (days)	9.8 ± 18.5 (2-11.5)	7.7 ± 8.4 (1.5-10.5)	0.421
Dialysis (%)	13 (35.2) (0.22-0.51)	18 (25.7) (0.17-0.37)	0.234
Dialysis (days)	6.2 ± 2.9 (4-9)	8.2 ± 6.1 (2.5-9)	0.063
In-hospital Mortality (%)	12 (32.4) (0.19-0.49)	18 (25.7) (0.17-0.37)	0.575
Only Aortic Operation	6 (27.3) (0.13-0.48)	8 (21.6) (0.11-0.37)	0.511
Add. Operation	6 (40.0) (0.19-0.64)	10 (30.3) (0.17-0.47)	0.493
Cause of Death (%)	12	18	
Thoracic Bleeding	3 (25.0) (0.09-0.53)	8 (44.4) (0.25-0.66)	0.05
Neurologic Failure	2 (16.7) (0.05-0.45)	1 (5.6) (0.01-0.26)	0.063
Cardiac Failure	5 (41.7) (0.19-0.68)	6 (33.3) (0.16-0.56)	0.392
Multivisceral Failure	2 (16.7)0.05-0.45)	3 (16.7) (0.06-039)	1

Categorical variables are expressed as rates ± 95% CI and continuous variables as mean ± SD and IQR (25° to 75° percentile); DHCA, deep hypothermic circulatory arrest; ACP, antegrade cerebral perfusion; IQR, interquartile range; ICU, intensive care unit; RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate. P<0.05 is statistically significant.

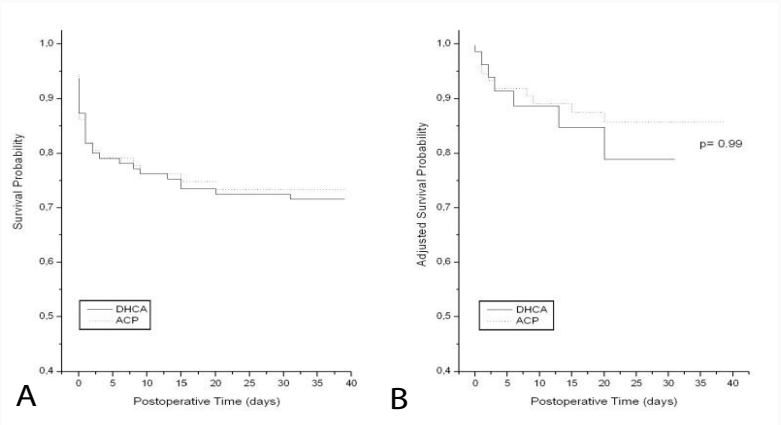

Figure 4: Kaplan-Meier representation of non-adjusted and risk-adjusted survival probabilities after aortic arch replacement. Kaplan-Meier survival analysis for patients receiving DHCA or ACP non-adjusted (4A) and adjusted (4B) for all relevant risk factors. DHCA, deep hypothermic circulatory arrest; ACP, antegrade cerebral perfusion, p<0.05 is statistically significant.

for abdominal organ function were also similar in the two groups (ALT: 34.44 ± 28.44 *vs.* 29.19 ± 14.86, p=0.164; GGT: 51.26 ± 52.25 *vs.* 73.26±91.38, p=0.184; Bilirubin: 0.55 ± 0.20 *vs.* 0.59 ± 0.26, p=0.331; AP: 78.55 ± 25.62 *vs.* 42.00 ± 54.70, p=0.119; Lactate: 2.8 ± 3.9 *vs.* 2.5 ± 2.9, p=0.653; CK: 118.56 ± 101.02 *vs.* 161.68 ± 205.92, p=0.137; Creatinine: 1.48 ± 1.58 *vs.* 1.16 ± 0.49, p=0.069; BUN: 24.50 ± 17.85

Table 4: Impact of preoperative lactate and catecholamine supplementation on visceral function after aortic arch surgery by linear regression.

		DHCA			ACP		DHCA vs. ACP
	slope	95% CI	P	slope	95% CI	P	p
Pre-OP Lactate vs.							
Peak CK	376.6	83.19 - 669.9	**0.0134**	782.9	33.91 - 1532	**0.0406**	0.3141
Peak Lactate	1.303	0.8778 - 1.729	**<0.0001**	0.747	0.2768 - 1.218	**0.0023**	0.0808
Inotropic Sc. (AUC) vs.							
Peak ALT	0.012	0.0007 - 0.0238	**0.0376**	0.011	0.0022 - 0.0192	**0.0147**	0.8236
Peak BUN	0.001	0.0003 - 0.0019	**0.0109**	0.002	0.0008 - 0.0031	**0.0007**	0.1939
Peak CK	0.118	-0.252	**0.0661**	1.262	1.001 - 1.523	**<0.0001**	**<0.0001**
Peak Lactate	0.001	0.0004 - 0.0007	**<0.0001**	0.0004	0.0003 - 0.0007	**<0.0001**	0.5882

DHCA: Deep Hypothermic Circulatory Arrest; ACP: Antegrade Cerebral Perfusion; CI: Confidential Intervals; P<0.05 is statistically significant

Table 5: Risk factors for in-Hospital Mortality in Cox Hazard Model.

		Univariate Analysis				Multivariate Analysis		
	b_i	HR	95% CI	P	b_i	HR	95% CI	P
Pre-OP Factors								
Ao. Dissection	2.318	10.2	1.38 – 74.5	**0.023**	0.889	2.43	0.27 – 22.9	0.432
Abd. Extension	-0.299	0.74	0.33 – 1.66	0.465				
Hem. Instable	1.391	4.02	1.88 – 8.58	**0.0003**	1.305	3.69	1.19 – 11.4	**0.023**
Pre-OP Lactate	0.013	1.01	1.00 – 1.02	**0.0003**	-0.029	1.00	0.99 – 1.01	0.566
Post-Sternot.	0.734	2.08	0.79 – 5.43	0.133				
Log. Euro-Score	0.032	1.03	1.02 - 1.05	**0.0001**	-0.012	0.99	0.96 – 1.02	0.456
Intra-OP Factors								
Cerebr. Protect.	-0.189	0.83	0.71 - 0.57	0.607				
Total arch repl.	-0.037	0.96	0.44 – 2.09	0.926				
Add cardiac OP	0.550	1.73	0.79 – 3.77	0.164				
Add root OP	0.372	1.45	0.71 – 2.94	0.307				
OP Time	0.003	1.00	1.00 – 1.00	**0.0001**	0.003	1.00	0.99 – 1.01	0.151
CPB Time	0.005	1.00	1.00 – 1.01	**<0.0001**	-0.003	1.00	1.00 – 1.01	0.511
Card. arr. Time	0.005	1.01	1.00 – 1.01	**0.034**	-0.001	1.00	0.98 – 1.00	0.809
Circ. arr. Time	0.001	1.00	0.98 – 1.01	0.981				
Temp <18°C	0.176	1.19	0.53 – 2.67	0.668				
Resternotomy	0.701	2.02	0.93 – 4.40	0.092				
Laparotomy	0.414	1.51	0.21 – 11.1	0.683				
Post-OP Factors								
Peak Inotr. Ind.	0.001	1.00	1.00 – 1.00	**<0.0001**	0.000	1.00	1.00 – 1.00	**0.006**
Inotr. Ind (AUC)	0.0001	1.00	1.00 – 1.00	**0.0004**				
Peak Lactate	0.019	1.02	1.01 – 1.03	**<0.0001**	0.017	1.02	1.01 -1.02	**0.0001**
Peak CK	0.0000	1.00	1.00 – 1.00	**0.033**	-0.000	1.00	0.99 – 1.00	0.191
Peak ALT	0.001	1.00	1.00 – 1.00	**0.012**	-0.001	1.00	0.99 – 1.00	0.186
Peak GGT	-0.003	1.00	0.99 – 1.00	0.071				
Peak Bilirubin	0.049	1.05	0.98 – 1.12	0.160				
Peak AP	0.0000	1.00	0.99 – 1.00	0.843				
Peak Creatinine	-0.015	0.98	0.96 – 1.01	0.199				
Peak BUN	-0.004	0.99	0.98 – 1.01	0.618				
Peak Leucocyte	-0.023	0.98	0.90 – 1.06	0.565				

vs. 25.00 ± 20.58, p=0.469; DHCA *vs.* ACP respectively).

Operative data

Intraoperative times and the extent of the surgical procedure were similar in both groups (Table 2), with the exception of circulatory arrest time that was a higher in the ACP group (p=0.003, Table 2). Surgical reinterventions did not differ between the two groups, including resternotomy for thoracic bleeding (p=0.587) and laparotomy for bowel resection (p=0.298). The resternotomy rate for acute cardiac failure with hemodynamic instability was slightly lower in the ACP group without reaching the level of significance (p=0.091). No significant differences in pre- or postoperative blood gas analyses were assessed between the groups (Supplemental Table 1).

Postoperative data

Postoperative ventilation time, inotropic support, need for dialysis, ICU- and hospital stay (Table 3) were similar in both groups. Cardiac function (documented in 11 DHCA and 21 ACP patients), post-operative transfusion requirements remained similar between the groups during the first postoperative week (Figure 1A,1B and Table 3). A significantly higher inotropic index was assessed in the DHCA group (Figure 1C) during the intensive care stay.

In-hospital mortality was slightly increased by additional surgery, whereas mortality related to cardiac failure and multivisceral dysfunction was similar in the two groups (Table 3). ALT, lactate and CK increased early (Figure 2), whereas GGT, Bilirubin and AP changed later in non-survivors (supplemental Figure 1). WBCs remained unchanged, whereas Creatinine and BUN changed randomly during the study period (supplemental Figure 2). The figures are presenting the mean laboratory values only at time-points where the data of at least 50% of the survivors were available. The preoperative lactate values and postoperative inotropic index (AUC) values were significantly lower in both ACP and DHCA survivor subgroups (Figure 3A,3B).

Risk factors analysis

The pre-operative lactate value was significantly associated with the maximal postoperative lactate and CK values in both ACP and DHCA groups (Table 4).

Inotropic score was associated with higher ALT, BUN, CK and Lactate values independently of cerebral protection technique. The type of cerebral protection and the extent of aortic arch replacement were unable to predict early mortality (Table 5). Neither the presence of aortic dissection (p<0.0001), nor operation- (p<0.0001), CPB- (p<0.001) and cardiac arrest (p<0.001) times - that were significant in the univariate analysis - altered the risk for death in the multivariate model. ALT and CK values - significant in the univariate analysis (p<0.05) - failed to demonstrate having an independent predictor capacity for death after aortic arch replacement. Hemodynamic instability (HR=3.69, p=0.023), maximal postoperative lactate value (HR=1.02, p=0.0001) and maximal postoperative inotropic score (HR=1.00, p=0.006) were associated with mortality in multivariate analysis.

Risk-adjusted survival curves for DHCA and ACP patients are depicted in Figure 4.

Discussion

The current study reports for the first time on temporal changes of biochemical markers for abdominal organ dysfunction after aortic arch repair under DHCA or ACP in an adult patient cohort with acquired aortic disease.

Mainstream risk scores for mutiorgan failure (SOFA, MODS, MOFA, Proulx) include Bilirubin and Creatinine levels as biochemical markers for abdominal organ dysfunction in critically ill patients [14-16] and have higher association with 90-day mortality whenever gastrointestinal dysfunction was included in the definitions of multiorgan failure (SOFA, Proulx). In the present study, ALT, Lactate and CK (Figure 2) illustrated early changes after aortic arch replacement whereas GGT, Bilirubin and AP (supplemental Figure 1) showed delayed modifications. Compliant with previous studies [17], changes in the early sensitive hepatic and intestinal markers occurred at similar time-points in all patients and were more accentuated in non-survivors. These findings suggest that the early ischemic injury before and during the surgical procedure causes an enhanced intestinal reperfusion damage that could further generate remote effects and influence the function of the other abdominal organs. The significance of the generally accepted risk scores for multiorgan failure remains doubtful in the early postoperative period after aortic arch surgery. Lactate at hospital admission was associated with postoperative non-occlusive mesenteric ischemia after cardiac procedure without circulatory arrest [18-20]. In an experimental model, base deficit was associated with the duration of preoperative cardiac resuscitation, but not with mortality [21]. In the present study, there were no significant differences in blood gases between the groups neither at the time of admission, nor postoperatively (supplemental Table 1 and Table 3) which conforms to the high percentage of hemodynamically stable patients in each group before the operation (Table 2). Studer et al. [22] demonstrated that different vasoconstriction drugs given during resuscitation can affect systemic and mesenteric perfusion and oxygenation during the post-resuscitation period with survivors being characterized by lower lactate levels. In consent, the present study reveals that survivors required less inotropic support than non-survivors in both DHCA and ACP groups (Figure 2B). Accordingly, the postoperative maximal lactate value – but not the preoperative lactate value – was identified as a risk factor for mortality (Table 5). The maximal postoperative inotropic score significantly correlated not only with the maximal postoperative lactate and CK levels, but also with the maximal postoperative ALT and BUN. This novel finding might suggest that the postoperative hemodynamic instability is more important in influencing postoperative abdominal organ function than the preoperatively pre-existing intestinal dysfunction. The linear relationship found between preoperative lactate value and the maximal post-operative lactate (p<0.0001 and p=0.002) and CK levels (p=0.01 and p=0.04) in DHCA and ACP groups respectively, confirm the prognostic value of preoperative lactate for the postoperative ischemia-reperfusion damage - independent from the type of cerebral protection used (Table 4). Nevertheless, preoperative lactate levels (p<0.0001) and maximal postoperative lactate (p<0.0001), CK (p=0.033) and ALT (p=0.012) values - significantly related to mortality in the univariate hazard model - failed to demonstrate a predictive value for early mortality in the multivariate analysis (Table 5). The univariate analysis revealed that operation time, CPB time and cardiac arrest time as possible risk factors for mortality (Table 5), whereas the multivariate analysis did not. Noteworthy, as presented in Table 2, none of the patients in the DHCA group and 2 patients in the ACP required bowel resection after aortic arch surgery. This finding entirely correlated with the preoperative presence of abdominal pain in the two cohorts.

These findings suggest that although operation-related abdominal ischemia-reperfusion injury, as revealed by the univariate analysis, may occur and influence outcome, deep hypothermic protection could counteract this effect and prevent additional occurrence of visceral ischemia. Moreover, multivariate analysis revealed that the impact of the length of cardiopulmonary bypass time on mesenteric circulation seems less important than the presence of short periods of hemodynamic instability as mirrored by the maximal postoperative lactate levels and by the catecholamine index (Table 5). In the case of aortic dissection [6-8], no significant difference was found in the visceral function of the groups undergoing different type of cerebral protection. In consent, preoperative aortic dissection might cause abdominal malperfusion, however surgical correction under hypothermia seems to limit its influence on postoperative outcome. Altogether, the present study reveals that both preoperative and postoperative hemodynamic instability have a significant prognostic value for mortality after aortic arch replacement (Table 5).

Prolonged DHCA negatively impacts respiratory, hemodynamic, and renal function [7]. Whereas increased DHCA duration was shown to adversely affect postoperative recovery, prolonged ACP was apparently without consequences [11]. Our present results revealed no differences in the ICU support of DHCA and ACP patients, indirectly suggesting application of the DHCA for shorter circulatory arrest times. Ischemia/reperfusion injury is an early postoperative phenomenon that depends of the preoperative lactate values and inotropic support (Table 4), and occurs independently of the type of cerebral protection used (Figure 2). This finding is reinforced by the Cox hazard model revealing no influence of type of perfusion on outcome (Table 5). Accordingly, risk-adjusted survival (Figure 4) did not differ significantly between the DHCA and ACP groups (p=0.99), suggesting that DHCA was applied to patients requiring shorter circulatory arrest times, whereas APC was used when longer arrest times were necessary (Table 2). In consent with previous findings [8], ACP was associated with a significantly lower inotropic score during the postoperative period (Figure 1C), emphasizing that the postoperative cardio-circulatory stability is more important in the protection against abdominal organ dysfunction than the degree of pre-existing malperfusion caused by dissection.

Limitations

There are several limitation to our analysis. First, there is a small number of cases included, mainly due to the lack of monitoring of the visceral parameters. Second, the data were analyzed retrospectively without a propensity match. As described previously, patients receiving ACP required longer circulatory arrest times. Therefore, this may be accounted for treatment bias that may influence the observed findings. Third, the fact that most of the patients in the ACP groups were operated under deep hypothermia provided the possibility to assess any additional but not alternative advantages offered by the ACP over DHCA. The lack of differences assessed between the groups in the risk-adjusted mortality may suggest application of ACP exclusively for longer periods of circulatory arrest. Although such characteristics may cause an underestimation of the remote protection offered by the ACP, we do not expect that this effect would be significantly superior to DHCA, since none of the patients in the DHCA group required bowel resection and revealed similar short-term survival.

Conclusion

Abdominal multiorgan dysfunction after open aortic arch surgery depends on the patient's preoperative and postoperative hemodynamic status and less on the extent of dissection and characteristics of the surgical procedure per sec. Importantly, ACP did not significantly influence the changes in the biochemical markers during the postoperative period, thus, a possible direct protective effect through improved arterial collateral circulation remains implausible in our setting. The present study cannot exclude an indirect long-term positive remote effect of ACP on the visceral function through improved central neurologic and cardio-circulatory homeostasis.

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