Survival, Neurologic Injury, and Kidney Function after Surgery for Acute Type A Aortic Dissection

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Abstract	Background To analyze survival, neurologic injury, and kidney function after acute
	type A aortic dissection.
	Methods A total of 445 patients undergoing surgery for acute type A aortic dissection
	were analyzed. Evaluation according to risk factors for mortality, neurologic injury, and
	kidney function was performed.
	Results Overall 1-, 5-, and 10-year survival rates were 82.8 \pm 1.8%, 73.6 \pm 2.4%, and
	59.3 \pm 3.9, respectively. Independent preoperative risk factors for mortality were
	preexisting renal impairment ($p = 0.001$), reduced left ventricular ejection fraction
	(p < 0.001), and age $(p < 0.001)$. Perioperative risk factors were prolonged cross-
	clamp ($p < 0.001$) and cerebral perfusion time ($p = 0.001$). Risk factors for renal failure
	were preexisting renal impairment ($p < 0.001$), prolonged cross-clamp time
	(p < 0.001), cerebral perfusion time $(p < 0.001)$, and age $(p = 0.022)$. Risk factors
	for neurologic injury were cross-clamp time ($p = 0.038$), cerebral perfusion time
	(p = 0.007), and age $(p = 0.045)$.
Keywords	Conclusion In addition to classic risk factors, survival after type A aortic dissection is affected
► aorta/aortic	by preexisting renal impairment. Preexisting renal impairment is predictive of postoperative
► database	renal failure. Therefore treatment and prevention strategies for renal failure during the acute
► kidney	and long-term course after acute type A aortic dissection are warranted.

Introduction

Outcome after surgery for type A aortic dissection has been continuously improving over the last decade.¹ Major conceptual improvements have been the routine use of the right subclavian artery for arterial inflow, selective antegrade

cerebral perfusion, and a trend toward less extensive core temperatures during hypothermic circulatory arrest.² Nevertheless, there is still room for improvement, in particular about neurologic outcome as well as about any type of preoperative malperfusion syndrome, as this is known to substantially affect the outcome.^{2,3}

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Table 1 Follow-up characteristics of the cohort

Total no. of patients	
Sum of follow-up years	1,707
Follow-up > 3 mo or deceased	430
Follow-up > 3 mo	308
Information by patient	
Information by general practitioner	
Data from CCIF	41
Deceased patients	122
No follow-up > 3 mo	

Abbreviation: CCIF, computed clinical information system.

This study aims to analyze survival, kidney function, and neurologic injury after surgery for acute type A aortic dissection in a large single-center cohort.

Materials and Methods

Study Cohort and Follow-up Modality

We analyzed 445 patients having undergone surgery for acute type A aortic dissection in our institution between 2001 and 2013. In 2013 all expected alive patients were contacted and written informed consent was obtained. In case of inability to reach an individual, the last documented follow-up available in our records was used. The local ethics committee approved the study (KEK-ZH-Nr. 2012–0039). The contact algorithm is shown in **-Table 1**. Descriptive characteristics of the patient cohort are given in **-Table 2**. Median follow-up was 3.0 (range: 0–12.5) years.

Anesthesiologic Management

Patients did not receive any premedication as for emergency procedure. Anesthesia induction and maintenance were standardized for all cases. A rapid sequence induction with midazolam (0.05-1 mg/kg), etomidate (0.2 mg/kg), for hemodynamic unstable patients or propofol bolus (1-3 mg/kg) for hemodynamic stable patients, with fentanyl (5 μ g/kg), and rocuronium (1 mg/kg) was used. Anesthesia was maintained with Sevorane (1.5-3 vol%) or propofol (2-3 µg/mL), continuous perfusion of remifentanil (0.1-0.5 µg/kg/min), and additional boli of rocuronium as needed. Anesthetic monitoring included American Society of Anesthesiologists routine monitors, two to three invasive blood pressures of the upper and/or lower extremities (via the left and right radial and femoral arteries), nasopharyngeal, and bladder temperature measurements. A four-lumen central venous catheter (7 F; Arrow, Reading, Pennsylvania, United States) and sheath (8.5 F; Arrow) were placed in the right internal jugular vein. At the end of anesthesia induction, a multiplane transesophageal echocardiography probe was inserted (Philips Medical Systems, Andover, Massachusetts, United States). Intraoperative, cerebral perfusion was monitored with continuous bilateral near-infrared oximetry (NIRS-Invos, Covidien, Mansfield, Massachusetts, United States). The simultaneous performance of a processed electroencephalogram (BIS, Aspect Medical Systems, Norwood, Massachusetts, United States) allowed the confirmation of burst suppression before initiation of hypothermic circulatory arrest. After median sternotomy, heparin (500 IU/kg) was given to achieve an activated clotting time of more than 350 seconds before cardiopulmonary bypass (CPB) and 500 seconds during bypass, with additional boli of 5000 to 10,000 IU if the activated clotting time did not reach the target values. CPB was primed with 10,000 IU of heparin. Simultaneously with heparin, tranexamic acid (30 mg/kg, maximal dose of 2 g) was administered intravenously. Therefore, besides premedication, anesthesiologic management was comparable to standardized management as published elsewhere.⁴

Conduction of Extracorporeal Circulation and Myocardial Protection Strategy

Patients were cooled to 20°C nasopharyngeal temperature and between 26°C and 28°C bladder temperature. Vasodilators such as phentolamine were used to achieve homogeneous cooling by reducing peripheral vascular resistance. During rewarming, targets were 36°C nasopharyngeal temperature and 35°C core temperature, comparable to strategies published elsewhere.⁴ Cardioplegia was given as to institutional standards. After termination of ECC, reversal of heparin with a protamine ratio of 1:1 (1 mg protamine per 100 IU heparin) was performed. An intraoperative autologous transfusion device with reinfusion of shed mediastinal blood and remaining ECC blood was frequently used. Intraoperative and postoperative transfusion regimens and coagulation management were guided by in-hospital standards (institutional algorithm) following rotational thromboelastometry (ROTEM, Pentapharm GmbH, Munich, Germany) and laboratory analysis of selected parameters of coagulation.

Definition of Clinical Parameters

Preoperative parameters were defined according to Euro-SCORE guidelines.⁵ Evaluated outcomes included longterm morbidity and mortality. Morbidity focused on postoperative renal failure with need for dialysis and occurrence of stroke (ischemic and hemorrhagic). Preoperative renal impairment was defined as preoperative creatinine greater than 200 µmol/L. No patient of the entire cohort was on renal replacement therapy prior to acute type A aortic dissection. Postoperative dialysis was stratified into need for acute (new onset of dialysis) or chronic renal replacement therapy for longer than 1 year after surgery or until death. The long-term setting had been appointed to exclude influences from concomitant effects of the acute setting, for example, distributive shock, sepsis, and malperfusion. Neurologic injury was defined as any newly developed sensorimotor deficit persisting at any point of follow-up combined with a morphologic correlate in cranial computed tomography. This definition of stroke was formulated to be conservative, considering that not all patients had routine neurologic consults postdissection. No evaluation of spinal cord ischemia was performed.

Table 2 Descriptive characteristics of the cohort $(n = 445)^a$

Demographics	
Age, mean, SD, y	62.7 ± 13.3
Age > 70 y, n (%)	148 (33)
Age > 80 y, n (%)	35 (8)
Female, n (%)	122 (27)
Chronic health conditions and risk factors	
Chronic obstructive pulmonary disease, n (%)	47/436 (11)
Renal impairment (creatinine $>$ 200 μ mol/L), <i>n</i> (%)	27/439 (6)
Diameter ascending aorta $>$ 45 mm, <i>n</i> (%)	277/440 (63
Arterial hypertension (RR syst $>$ 140 mm Hg), <i>n</i> (%)	296/379 (78
Diabetes mellitus, n (%)	21/242 (9)
BMI, mean, SD	26.8 ± 4.6
Preoperative assessment	
EuroSCORE, additive, mean, SD	11 ± 3
Redo surgery, n (%)	22 (5)
Preoperative tamponade, n (%)	64/440 (15)
Left ventricular dysfunction (LVEF $<$ 55%), n (%)	191/420 (46
Left coronary artery affected by dissection, <i>n</i> (%)	31/440 (7)
Right coronary artery affected by dissection, <i>n</i> (%) Cardiogenic shock	57/440 (13) 45/442 (10)
Intraoperative assessment	
Cross-clamp time (min), median, (IQR)	91 (55)
Total circulatory arrest time (min), median, (quartile 3)	2 (17)
Selective cerebral perfusion (min), median, (IQR)	28 (20)
Antegrade cerebral perfusion, n (%)	375/414 (91
Retrograde cerebral perfusion, n (%)	12/406 (3)
Extent of operation	· · · · · · · · · · · · · · · · · · ·
Valve	
Bentall procedure, n (%)	125/445 (28
Resuspension, n (%)	138/445 (31
Arch	
Hemiarch replacement, n (%)	240/445 (54
Total arch replacement, n (%)	50/445 (11)
Postoperative assessment	· · · · ·
Freedom from dialysis, n (%)	390/437 (89
Freedom from long-term dialysis, n (%)	416/435 (96
Freedom from reoperation, n (%)	404/445 (9
Freedom from ischemic stroke, n (%)	373/440 (85
Freedom from hemorrhagic stroke, <i>n</i> (%)	421/428 (98

Abbreviations: BMI, body mass index; IQR, interquartile range; LVEF, left ventricular ejection fraction; RR, relative risk; SD, standard deviation; syst, systolic.

^aMissing data lead to varying total numbers.

Statistical Methods

Freedom from events was analyzed using Kaplan–Meier curves and reported as estimate at 1, 3, 5, and, if reasonable, 10 years \pm standard error. Groups were compared using

the log-rank test. The effect of continuous and binary variables was analyzed using univariate Cox-regression. Odds ratios (OR) are reported with 95% confidence intervals (CI). A multivariable logistic model was applied to assess

Table 3 Univariate analysis of overall mortality

Risk factor	OR	95% CI	p Value
Chronic obstructive lung disease	1.533	0.924-2.541	0.098
Creatinine > 200 µmol/L	2.176	1.193–3.97	0.011
Diameter ascending aorta $>$ 45 mm	0.901	0.59–1.377	0.630
Arterial hypertension	1.817	0.991-3.331	0.054
Diabetes mellitus	1.1	0.463-2.608	0.83
Affected left coronary artery	1.369	0.751–2.497	0.305
Affected right coronary artery	1.378	0.842-2.257	0.202
Redo surgery	1.628	0.847-3.129	0.144
Cross-clamp time	1.006	1.003-1.009	< 0.001
Cerebral perfusion time	1.015	1.006-1.024	0.001
Impaired left ventricular function	0.965	0.945-0.986	0.001
EuroSCORE	1.168	1.059–1.289	0.002
BMI	1.003	0.962-1.046	0.88
Age	1.037	1.021-1.054	< 0.001

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

independent preoperative risk factors for overall outcome. We considered age, renal impairment, and reduced left ventricular ejection fraction, the preoperative risk factors that were statistically significant in univariate analysis for inclusion. EuroSCORE levels as a score of different factors was not considered for multivariate analysis. With regard to fewer events of postoperative neurologic and renal impairment, no appropriate multivariate analysis was possible for these morbidity aspects. Analysis was performed using IBM SPSS Statistics (Version 22. Armonk, New York, United States).

Results

Survival

Overall, 1-, 5-, and 10-year survival rates were 82.8 \pm 1.8%, 73.6 \pm 2.4%, and 59.3 \pm 3.9, respectively. Preoperative renal impairment (p = 0.011), higher age (p < 0.001), reduced left ventricular ejection fraction (p = 0.001), higher numeric EuroSCORE levels (p = 0.002), longer cross-clamp times (p < 0.001), and longer cerebral perfusion times (p = 0.001) were predictors of mortality at any time point during follow-up (**-Table 3**). In the multivariate analysis (**-Table 4**) preoperative renal impairment (p = 0.001), higher age (p < 0.001), and reduced left ventricular ejection fraction (p < 0.001) were independent preoperative risk factors for mortality. No significant distribution difference was observed between patients with or without critical preoperative status in terms of elevated creatinine levels greater than 200 μ mol/L (p = 0.077). Up to 4 years survival curves diverge between patients with and without preoperative elevated creatinine levels. After 4 years only few patients at risk are left in the preoperative elevated creatinine group (►Fig. 1).

The total number of deaths was 120. Detailed in-hospital records from 62 patients were available. Of these, 41 deaths were aortic and 9 cardiac related. Three were due to infection and three to bleedings. Six patients had other causes of death. 58 patients died during follow-up in an ambulant setting. No detailed medical reports or autopsy results were available for these patients.

Dialysis

Overall risk for new dialysis was $6 \pm 1.8\%$, $10 \pm 1.7\%$, and $13 \pm 2\%$ within 1, 3, and 5 years after surgery for acute type A aortic dissection. Preoperative renal impairment (p < 0.001), higher age (p = 0.022), higher numeric EuroSCORE levels (p = 0.022), and prolonged cross-clamp and cerebral perfusion times (p < 0.001; p < 0.001) were predictive for the need of perioperative dialysis (**-Table 5**).

Predictors for long-term dialysis were preoperative renal impairment (p < 0.001) and prolonged cross-clamp and cerebral perfusion time (p < 0.001; p < 0.001), (**-Table 6**). No statistical evaluation was possible for patients with chronic obstructive pulmonary disease (COPD), affected left or right coronary ostium, or redo surgery due to low event rate. Overall risk for long-term dialysis was $3 \pm 0.7\%$ and $5 \pm 1.3\%$ within 3 and 5 years, respectively, after surgery for acute type A aortic dissection.

Neurologic Impairment

Overall estimated 1-, 3-, and 5-year freedom from neurologic impairment was 90 \pm 1.5%, 87 \pm 1.7%, and 84 \pm 2.1%, respectively. Higher age (p = 0.045) and prolonged cross-clamp and cerebral perfusion time (p = 0.038; p = 0.007) were predictors for disabling stroke (**-Table 7**). Seven hemorrhagic strokes occurred during the complete postoperative period (10% of all events).

Risk factor	OR	95% CI	p Value
Creatinine > 200 µmol/L	2.858	1.532–5.335	= 0.001
Impaired left ventricular function	0.443	0.296-0.664	< 0.001
Age	1.050	1.032–1.069	< 0.001

 Table 4
 Multivariate analysis of preoperative predictors for overall mortality

Abbreviations: CI, confidence interval; OR, odds ratio.

Discussion

In addition to classic risk factors, survival after type A aortic dissection is affected by preexisting renal impairment. Risk factors for any neurologic injury also during follow-up were age and prolonged cross-clamp and cerebral perfusion time. Preexisting renal impairment is predictive of any postoperative renal failure.

Overall 1-, 3-, 5-, and 10-year survival rates were estimated 83%, 78%, 74%, and 59%, respectively. The initial attrition rate is primarily due to the event of acute aortic dissection per se and related problems in untreated segments of the aorta as well as to cardiac disease, as indicated from 62 detailed inhospital medical records from death patients in our cohort. Most series addressing surgery for acute type A aortic dissection focus on perioperative outcome and often lack reporting of survival greater than 4 years.^{3,6–10} The few contemporary trials with longer follow-up show comparable outcomes.¹¹ However, patient number reported is substantially smaller in most studies.

Renal impairment, higher age, and reduced left ventricular ejection fraction were independent preoperative predictors of mortality. Impaired renal function has been confirmed in patients with stroke,¹² coronary artery disease,¹³ diabetes,¹⁴ hypertension¹⁵ and in the general population¹⁶ as an independent predictor of mortality. However, no other trial had focused on preoperative renal impairment in patients with acute type A aortic dissection to date. We identified preoperative renal impairment as an independent predictor for mortality in surgically treated patients with acute type A aortic dissection. This finding was independent from critical preoperative state, so we presume not only the acute impairment in the setting of acute cardiogenic shock or as an entity of malperfusion syndrome with potential reversal after correcting the underlying pathological mechanisms but also the long-term manifestation of renal disease affects survival. We suggest that the pathophysiologic processes underlying vascular endothelial dysfunction due to renal disease may explain our findings. This is supported by the aspect that over the first years survival curves with subject to preoperative

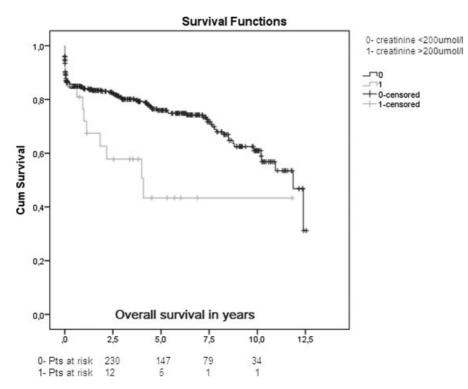


Fig. 1 Kaplan-Meier curve of overall survival subject to preoperative renal impairment. Pts, patients.

 Table 5
 Univariate analysis of overall new dialysis

Risk factor	OR	95% CI	p Value
Chronic obstructive lung disease	0.943	0.288-3.092	0.923
Creatinine > 200 µmol/L	5.278	2.277-12.235	< 0.001
Diameter ascending aorta > 45 mm	0.836	0.391–1.785	0.644
Arterial hypertension	0.756	0.339–1.687	0.495
Diabetes mellitus	0.704	0.199–2.485	0.585
Affected left coronary artery	0.356	0.049-2.605	0.309
Affected right coronary artery	0.415	0.099–1,732	0.228
Redo surgery	1.735	0.530-5.6778	0.363
Cross-clamp time	1.011	1.006-1.015	< 0.001
Cerebral perfusion time	1.029	1.018-1.040	< 0.001
Impaired left ventricular function	0.996	0.962-1.032	0.84
EuroSCORE	1.164	1.021–1.326	0.022
BMI	1.023	0.986-1.081	0.42
Age	1.028	1.004–1.054	0.022

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

renal impairment diverge. Therefore these findings are different to data reported by Tsai et al. who detected that acute kidney injury 24h after surgery is an important predictor of mortality.¹⁷ One trial reported preoperative serum creatinine values¹⁸ but found no significant change in mortality with higher serum levels. Most important, different definitions of renal impairment may have led to these results. Our trial addressed patients with a KDIGO 2012 class G3b-4 (moderate to severe impaired renal function), whereas Pagni et al¹⁸ used a creatinine cutoff of larger than 1.4 mg/dL, reflecting a mild to moderate impaired renal function (KDIGO class G2 to G3a). Lower total numbers (132 vs. 445 patients in our trial) and inclusion of nonsurgically managed patient might be additional confounding factors.

Our finding that impaired left ventricular function is an independent risk factor is supported by current literature.¹⁸

The discussion regarding age and outcome in acute type A aortic dissection has several aspects. As most studies do not report their exclusion criteria for subjecting or nonsubjecting elderly patients for surgery, outcomes might be somewhat biased as merely the biologically fittest will gain access to treatment. This might account for the fact that advanced age is a risk factor in several reports as it is not in others. Finally it has to be mentioned that the overall number of octogenarians in all series is low. Longer cross-clamp time and prolonged cerebral perfusion time reflecting the extent of disease are prescribed as risk factors previously and consistently in current literature.¹⁸

Table 6	Univariate anal	ysis of long-term	dialysis (> 1	year after op	peration or until death)
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Risk factor	OR	95% CI	p Value
Creatinine > 200 µmol/L	15.636	3.775-64.765	< 0.001
Diameter ascending aorta $>$ 45 mm	1.053	0.193-5.761	0.952
Arterial hypertension	1.534	0.189–12.524	0.688
Diabetes mellitus	2.272	0.276-18.731	0.446
Cross-clamp time	1.011	1.006–1.018	< 0.001
Cerebral perfusion time	1.031	1.014-1.048	< 0.001
Impaired left ventricular function	0.987	0.936–1.041	0.63
EuroSCORE	1.033	0.814-1.311	0.79
BMI	0.993	0.888-1.111	0.90
Age	1.006	0.971–1.043	0.72

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Risk factor	OR	95% CI	p Value
Chronic obstructive lung disease	1.318	0.557-3.120	0.530
Creatinine > 200 µmol/L	0.923	0.222-3.826	0.912
Diameter ascending aorta > 45 mm	0.899	0.459–1.758	0.755
Arterial hypertension	1.018	0.485-2.138	0.962
Diabetes mellitus	0.639	0.184-2.219	0.480
Affected left coronary artery	0.236	0.032-1.720	0.154
Redo surgery	0.704	0.667–2.959	0.632
Cross-clamp time	1.005	1.000-1.010	0.038
Cerebral perfusion time	1.016	1.005–1.028	0.007
Impaired left ventricular function	1.007	0.975–1.040	0.67
EuroSCORE	0.980	0.863-1.113	0.75
BMI	0.937	0.877-1.001	0.061
Age	1.020	1.000-1.040	0.045

Table 7 Univariate analysis of neurologic impairment

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Overall risk for new dialysis was 6% in the first year after surgery and 13% in the 5 years after surgery for acute type A aortic dissection. Risk factors for postoperative dialysis were preoperative renal impairment, higher age, higher numeric EuroSCORE levels, and prolonged cross-clamp and cerebral perfusion times. Tsai reported that 11.2% of his patients with surgically treated type A or B aortic dissection received temporary dialysis during the initial hospital stay after surgery.¹⁹ In a recent report, hypertension, lower limb malperfusion, and sepsis were independent risk factors for postoperative renal failure,¹⁷ but again only in the acute setting after aortic dissection. Several risk factors in the initial postoperative period (e.g., sepsis, malperfusion) lead to temporary need for dialysis, but with sufficient treatment, long-term need for renal replacement therapy should be avoidable. Of note no trial reporting on longterm dependency of dialysis after surgery for acute type A aortic dissection is available in current literature. To differentiate between temporary and prolonged need for dialysis, a second analysis was done only for patients with prolonged (> 1 year after surgery or until death) need for dialysis. After 5 years the risk of long-term dialysis was 5%, and therefore substantially lower than the overall risk of new dialysis. Predictors for long-term dialysis were preoperative renal impairment and prolonged cross-clamp and cerebral perfusion time. Therefore, beside the extent of the disease, reflected by cross-clamp and cerebral perfusion time, preoperative renal impairment was responsible for a key factor of long term morbidity. Beside this, renal failure is an important risk factor for a broad range of other diseases, so treatment strategies in patients with postoperative renal impairment are crucial. Therefore blood pressure control and restoring renal blood flow in acute and subacute setting as well as treatment of an eventually underlying renal disease are of importance to decrease need for dialysis.

Overall estimated 1- and 5-year freedom from strokerelated neurologic impairment was 90% and 84%, respectively. The IRAD study group reported a total of 6% of patients with acute type A aortic dissection presenting with stroke initially.¹⁰ Aim of the surgery for acute type A aortic dissection with cerebral malperfusion is to restore cerebral perfusion that may resolve neurologic deficits. Pagni reported an incidence of 13.6% of postoperative stroke, with no definition for stroke given in the paper.¹⁸ Taken the emergency situation prior to operation into account with patients often arriving intubated in our tertiary care center and even lacking data about a complete preoperative neurological status, we focused on postoperative neurologic outcome. Therefore both preoperative neurologic complications and surgical risk factors have to be considered. Higher age and prolonged cross-clamp and cerebral perfusion time were predictors for disabling stroke in our analysis. The prospective analysis of neurologic dysfunction by Conzelmann and colleagues in GERAADA²⁰ showed a similar pattern for duration of cardiopulmonary bypass and circulatory arrest. Other risk factors for postoperative stroke like malperfusion and dissection of the supra-aortic vessels²⁰ were not analyzed in our study. Beside age, no other examined preoperative condition met significance in our study.

Clinical Implications

Trials for treatment of renal failure should include acute aortic dissection as a composite outcome intended to determine the overall impact of the treatment to investigate strategies (blood pressure control, improvement of lower limb perfusion) to positively influence pre- and postoperative renal impairment and lower mortality rate. Especially in high-risk patients aggressive prevention is substantial and therefore therapy addressing the most relevant risk factors is necessary. Further demographic changes will lead to increased event rates during the next years.

Study Limitations

Like any retrospective review, this study has limitations. It is a cohort of unselected patients and the denominator of patients that declined or were not offered surgery is unknown. Our technique has evolved over the study period (i.e., cannulation site, root replacement type, surgical skill, cerebral perfusion) and results might also be affected by the different surgeons involved. With regard to neurologic impairment, no evaluation of spinal cord ischemia was performed and no evaluation targeting different surgical techniques or cerebral malperfusion imaging took place.

Conclusion

In addition to classic risk factors, survival after type A aortic dissection is affected by preexisting renal impairment. Risk factors for any neurologic injury also during follow-up were age and prolonged cross clamp- and cerebral perfusion time. Finally, preexisting renal impairment is predictive of any postoperative renal failure and therefore important for long term morbidity. Consequently, treatment and prevention strategies for renal failure during the acute and long-term course after acute type A aortic dissection are warranted and continuous monitoring of these patients remains mandatory.

Conflict of Interest None.

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