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Original study

The incidence of early neurological complications after on-pump cardiac surgery: a retrospective study

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Abstract

Background: **Cardiac surgery with cardiopulmonary bypass (CPB) is associated with a significant risk for neurological complications. Reported incidence and risk factors for these complications vary significantly. Identifying risk factors could lead to preventive strategies to reduce complications and improve patient's outcome.**
Objective: **The study aims to assess the overall incidence and risk factors for severe early postoperative neurological complications after elective on-pump cardiac surgery. We specifically analyzed the incidence of stroke, global cerebral ischemia (GCI) and epilepsy in these patients.**
Methods: **After getting approval from the Ethics Committee Research UZ/KU Leuven, on 14/12/2021 (s65871), we retrospectively evaluated data of 1080 adult patients after cardiac surgery with CPB between 06/2019 and 06/2021 at the University Hospitals Leuven. After exclusion of emergency procedures and patients who died before neurological evaluation, 977 patients remained for primary analysis. All data were collected from the electronic patient's file. Primary objective was to identify the incidence of stroke, GCI and epilepsy. We defined stroke and GCI according to the American Stroke Association. Secondary endpoints were identifying independent risk-factors and assessing the impact of early neurological complications on mortality. Statistical analysis was performed using econometric and statistical modeling with python. We performed univariate logistic regression with Bonferonni correction and multivariable logistic regression with backwards elimination approach and p-value set to be <0.05.**
Results: **The overall incidence of defined neurological complications after elective on-pump cardiac surgery at our institution was 3.17% (n=31) (stroke 2.35% (n=23), epilepsy 0.61% (n=6) and GCI 0.31% (n=3)). No statistically significant risk factors for these complications were found. In secondary analysis, patients with stroke and GCI had a higher risk of in-hospital mortality (Fisher's exact test resulted in odds ratio 7.23 with p=0.005 and odds ratio 65.17 with p=0.003 respectively) Diabetes mellitus, preoperative atrial fibrillation, and endocarditis were also significantly related to in-hospital mortality.**
Conclusions: **The incidence of early neurological complications after elective on-pump cardiac surgery at our institution was comparable to that reported in earlier studies. No independent risk factors for these neurological complications were found. The occurrence of stroke and GCI significantly increased in-hospital mortality which emphasizes the importance of these complications, with possible mortality benefit of early recognition and management of stroke.**

Keywords: **Cardiopulmonary bypass, Cardiac surgical procedures, Stroke, Epilepsy, Encephalopathy.**

Introduction

Neurological complications are quite common after cardiac surgery, with significant morbidity and mortality. These complications often manifest in the early postoperative period, but can also present later during hospitalization or after hospital discharge. Stroke, epilepsy, cerebral encephalopathy, global cerebral ischemia (GCI), postoperative delirium, and postoperative cognitive dysfunction are examples of these neurological impairments[1–4].

The pathogenesis of most of these complications is probably multifactorial and is not always clear. Guidelines to reduce these neurological complications have not been developed yet. Other studies have assessed the incidence of postoperative neurological complications and risk factors in patients undergoing cardiac surgery. Nevertheless, the results are conflicting because of several reasons, such as a low number of complications, small sample size, different surgical approaches and patient population, diverse intraoperative anesthetics, and different inclusion criteria[1,5–9].

The purpose of the current retrospective study was to investigate the overall incidence and risk factors of early severe post-operative neurological complications after on-pump cardiac surgery at the University Hospitals Leuven. In particular, we assessed the incidence of in-hospital stroke, global cerebral ischemia (GCI) and epilepsy. We chose to specifically investigate these complications because they have a significant impact on outcome, and are well documented to allow retrospective study. The secondary aims were to identify independent risk-factors for these complications and assess their impact on patient's morbidity and mortality. Identifying significant risk factors could lead to the development of preventive measures. We studied only (semi-) elective patients, to exclude the influence of a critical preoperative state.

Materials and methods

Study population and design

We retrospectively evaluated pre-, per- and postoperative data of 1080 adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) in the University Hospitals Leuven between 01/06/2019 and 31/05/2021. Patients older than 18 years and scheduled for elective on-pump cardiac surgery were included.

Exclusion criteria were: patient's age < 18 years, no CPB, emergency surgery (operated within 24h), congenital heart defects, and death before neurological evaluation. Patients who died during surgery or before a neurologic evaluation was conceivable (before extubation), were excluded from primary analysis but included for the exploratory analysis of in-hospital mortality.

Board approval of the Ethics Committee Research UZ/KU Leuven was gained, with a waiver for individual consent. Ethics Committee Research UZ/KU Leuven, Herestraat 49, 3000 Leuven. Reference number s65871. Approved by Prof. Dr. Minne Casteels on 14/12/2021.

This manuscript adheres to the applicable STROBE guidelines [10].

Study aims

The primary aim of the present study was to identify the incidence of in-hospital postoperative severe neurological complications; defined as stroke, GCI and epilepsy, after on-pump elective cardiac surgery. The secondary aims were to identify independent risk-factors for these complications, and asses their impact on mortality.

Data collection

A patient list was acquired from the department of cardiac surgery which contained all cardiac surgeries with CPB in patients older than 18 years, from 01/06/2019 to 31/05/2021.

Patient data was pseudonymized and further data collected retrospectively from the electronic patient file based on the hospitalization report. The collected patient data was selected based on being identified as risk factors in previous studies, and being reliably documented for retrospective analysis.

Diagnosis of neurological complications was based on documentation of clinical signs, evaluation by neurologist, and neuroimaging

We defined stroke according to the 2013 definition of the American Stroke Association as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury[11]. If there were clinical signs of neurologic deficit, and neuroimaging showed recent infarction or hemorrhage, we defined this as stroke.

Global cerebral ischemia (GCI) was also defined according to the American Stroke Association, as diffuse cerebral damage due to hypoperfusion, not defined to a specific vascular distribution. If patients had nonspecific neurological dysfunction, bilateral diffuse ischemia on imaging defined by a radiologist and/or neurologist as global ischemia, or ischemia due to diffuse hypoperfusion, we defined this as GCI.

An epileptic complication/seizure was defined as a witnessed generalized clonic insult or partial insult with or without EEG confirmation and validated by a neurologist as a probable epileptic insult. Patients who experienced an epileptic insult after cerebral ischemia were also registered as epilepsy, but only counted once for the incidence of overall neurological complications.

Other complications such as delirium, pneumonia and kidney injury, were registered if they were documented in the hospitalization report. No specific diagnostic criteria were used.

Surgical techniques

All cardiac procedures were performed in an elective or semi-elective condition. All surgeries used CPB controlled by a trained perfusionist. All patients were evaluated perioperatively with transesophageal echocardiography. Depending on the surgery, different surgical techniques were used. Most often, a central sternotomy was performed. Some operations were performed using a minimally invasive approach. Aortic cannulation for CPB was performed centrally (through the aorta) or peripherally (through femoral or subclavian artery). Venous cannulation for CPB was also inserted centrally by cannulation of the right atrial appendage, the right atrium, the superior and or the inferior vena cava or peripherally via femoral vein[12,13]. An aortic cross clamp and cardioplegia were used in most of the procedures. All procedures used intraoperative cell salvage to recover blood back from pericardial suctioning, although this blood was not transfused back in all patients.

All patients were fully heparinized while on CPB, with ACT > 480sec. and fully reversed by protamine in a one to one ratio at the end of surgery.

Statistical analysis

In total, 1080 patients were screened for primary analysis of neurological complications.

Demographic and patients' characteristic data were analyzed using a commercially available statistical software package (see below). Continuous variables were reported using mean and standard deviations and compared using a student t-test. In case of deviations from the normal distributions, as assessed by the Shapiro-Wilk test, the data was described using median and interquartile range [IQR] and compared using Mann-Whitney test. Categorical data were summarized by total number and percentages and compared using Chi-squared or Fisher's exact test, when appropriate.

For the analysis of mortality, patients who were excluded from primary analysis due to death before neurological evaluation were included (i.e., mortality set). For the analysis of "Aorta clamp time", only the subset of patients who had an arterial cross clamp during surgery were included. The incidence of postoperative atrial fibrillation (A-fib) was only registered in patients without history thereof (i.e., new-onset of A-fib).

The association of each potential risk factor (patient-, anesthesia- and operation related) with the risk for (overall and specific) neurological complications was evaluated using univariate logistic regression with maximum likelihood estimation. Odds ratios and their 95% confidence intervals with corresponding p-values were calculated. Statistically significant correlations (i.e., $p < 0.05$) were subjected to a Bonferroni correction, to correct for multiple hypothesis testing. The same analysis was repeated for overall mortality on the mortality set.

Multivariable logistic regression was performed using a backwards elimination approach for feature selection with a p-value for significance set to 0.05. Categorical variables were converted to binary variables by using dummy labels. Optimization algorithms for loss minimization which avoid errors due to non-invertibility of Hessian matrices were implemented for the regression analysis.

Additionally, a Lasso logistic regression approach for feature selection was performed to compare the resulting variables from the backwards elimination approach. Missing values were substituted by mean values. Numerical variables were normalized to equalize the penalization scheme to all regressors. The value for the weight given to the L1 regularization term (α) was tuned to end up with the same number of variables with non-zero coefficient as for the backwards elimination algorithm.

Results of repeated multivariable logistic regression with the selected features were reported with a receiver operating characteristic (ROC) curve and the area under the curve (AUC). Using this resulting model, outcome predictions can be made based on the values for the selected input variables. For analyses of direct correlations between categorical variables, the Chi-squared test of independence was performed. If any value lower than five was present in the contingency table, Fisher's exact test was used instead.

All statistical analyses were performed with Python's statsmodel 0.11.0 14, Scikit-learn 0.22.1[15], and SciPy 1.4.1[16] packages or in R.

Results

After exclusion of patients who did not meet the selection criteria, 977 patients were included for the primary outcome. Mean age was 68±12 years, 60% of patients were male (n=591), 40% female (n=386). Patients' demographics, surgery-related and postoperative complications are presented in Table I. Moreover, distribution of cardiac procedures is presented in figure 1.

Incidences

The overall incidence of severe neurological complications was 3.17% (n=31), of which 2.35% presented with stroke (n=23), 0.31% with GCI (n=3), and 0.61% with epileptic activity (n=6, of which one patient also had GCI). We did not find a significant difference in complication rate between the different surgery groups. All 31 patients with neurological complications had a brain CT, 17 of these patients had an additional MRI of the brain.

All three patients with GCI showed new ischemia on neuro-imaging. Of the cases with epilepsy, two patients (with status epilepticus) showed new ischemia. Of the 23 patients with stroke, only one did not show new findings on brain CT (no MRI was performed) and one patient showed hemorrhagic findings. All 21 other patients with stroke showed new ischemia on CT or MRI.

Among the patients with stroke, hemispheric side of ischemia on imaging was evenly divided (eight left sided, seven right sided, eight bilateral). Symptoms were present immediately after extubation in 61% of the patients with stroke (n=14), while 39% presented with symptoms during the following days (n=9). All three patients with GCI presented with symptoms immediately after extubation and showed bilateral ischemia on imaging. Two of these patients died during admission to the ICU, the third patient remained care dependent. Of the patients with epilepsy, three were diagnosed with status epilepticus, of which one was also diagnosed with global cerebral ischemia (and remained care dependent). All other patients recovered completely without later documented seizures.

Morbidity and mortality

In the primary analysis set (i.e., excluding early deaths n=8 patients) post-operative mortality was 3.17% (31/977). If we include early deaths, the post-operative mortality was 3.96% (39/985).
In the neurologic complications group, 19.35% (6/31) died during hospitalization (after extubation); 17.39% (4/23) of them had a stroke and 66.67% (2/3) had a GCI.

Most common other complications were: new-onset A-fib 37.08% (254/685, excluding patients who already had preoperatively documented A-fib n=292), postoperative delirium 14.12% (138/977), and acute kidney injury 26.1% (225/977). Revision surgery for tamponade or bleeding complications was performed in 4.81% (47/977).

The incidence of all post-operative complications is presented in figure 2.

Risk factors for neurological complications

Risk-factors related to neurological complications were:

Diabetes mellitus (DM, this includes type I and II diabetes) was the only variable to reach statistical significance with an odds ratio (OR) of 2.34 (95% CI 1.08-5.06, p=0.03). However, this result did not remain significant after Bonferroni correction. (Table II)

Length of ICU stay, readmission to ICU, days of ICU readmission, and total hospital length of stay also reached statistical significance, but can be

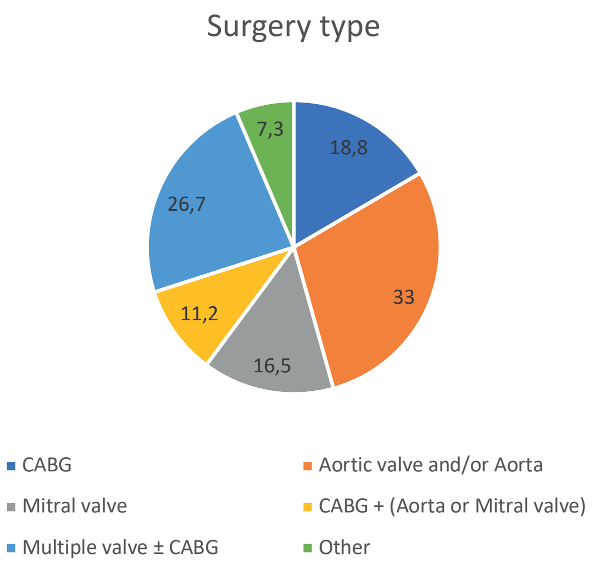

Fig. 1 — Percentage of different surgery type.

interpreted as a direct consequence of postoperative complications and are therefore considered as confounding factors. These variables are not considered in further analyses.

Individual neurological complications

Univariate logistic regression was repeated for the individual neurological complications stroke, GCI, and epilepsy. Only pre-operative A-fib was found to be significantly correlated with postoperative epilepsy (OR 11.93 (1.39-102.69), p=0.02). However, statistical significance was not kept after Bonferroni correction (Table II). Although the correlation of endocarditis with the incidence of stroke did not reach statistical significance, a certain trend seems to be present (OR 2.83 (CI 0.93–8.56), p=0.06).

Perioperative variables, including type of surgery, tranexamic acid use, CPB time, cannulation site and aortic clamp time, did not reach a significant correlation with the incidence of severe neurological complications (combined and separate).

Multivariable logistic regression analyses

The only remaining variable of the backwards elimination procedure with the default threshold p-value for significance of 0.05, was DM. Increasing the threshold from 0.05 to 0.15 resulted in a final model with variables DM, sex, multiple valve surgery, and CPB time as predictive for neurological complications. Further modest increments in p-value did not yield additional variables.

Risk factors for mortality

Univariate logistic regression for in-hospital mortality rendered statistical significance for the following variables: age (OR 1.04 (95% CI 1.005 – 1.07), p=0.02), arterial hypertension (AHT) (OR

Table I. — Patients characteristics, surgery-related and postoperative data. Continuous variables are presented with median and IQR. Binary variables are presented with number and percentage. N is the total number of patients analyzed in each group.

Variables	Patients without neurological complications				Patients with neurological complications			
Preoperative characteristics				N			N	P-value
Age (years)	Median and IQR	70	61-77	946	70	62.5-76	31	0.37
Weight (kg)	Median and IQR	78	67-88	946	73	62-88	31	0.21
Height (cm)	Median and IQR	170	162-177	946	170	164-177	31	0.36
Gender (M)	n (%)	576	60.89%	946	15	48.39%	31	0.22
Hypertension	n (%)	566	59.89%	945	20	64.52%	31	0.74
Diabetes	n (%)	160	16.91%	946	10	32.26%	31	0.05
Atrial fibrillation	n (%)	281	29.7%	946	11	35.48%	31	0.62
History of CVA/TIA	n (%)	80	8.46%	946	2	6.45%	31	1.00
Carotid stenosis > 70%	n (%)	21	2.93%	717	1	4.76%	21	0.51
Endocarditis	n (%)	66	6.98%	946	4	12.9%	31	0.27
Surgery type								
CABG	n (%)	50	5.28%	946	2	6.45%	31	0.68
Aortic valve ± Aorta	n (%)	310	32.77%	946	12	38.71%	31	0.62
Mitral valve	n (%)	157	16.6%	946	4	12.9%	31	0.81
CABG + Aorta or Mitral valve	n (%)	105	11.1%	946	5	16.13%	31	0.56
Multiple valve ± CABG	n (%)	256	27.06%	946	5	16.13%	31	0.25
Other	n (%)	68	7.19%	946	3	9.68%	31	0.49
Operative details								
CPB time (min)	Median and IQR	112	84-148	929	115	91.5-153	31	0.34
Clamp time (min)	Median and IQR	76	55-102	873	78,5	70-101.25	28	0.17
Cannulation site (central)	n (%)	726	77.56%	936	24	82.76%	29	0.66
Use of Tranexemic Acid	n (%)	315	36%	875	9	30%	30	0.63
Use of cardoplegia	n (%)	875	92.79%	943	28	90.32%	31	0.50
No aorta clamp used	n (%)	73	7.72%	946	0	0%	28	0.26
Post-operative data								
Length of ICU stay (days)	Median and IQR	2	0-4	946	7	2.5-11.5	31	<0.001
Length of hospital stay (days)	Median and IQR	9	7-15	946	27	10.5-47	31	<0.001
Readmission to ICU after discharge	n (%)	25	2.64%	946	3	9.68%	31	0.05
PACU admission	n (%)	334	35.31%	946	5	16.13%	31	0.04
Post-operative complications								
Mortality	n (%)	25	2.64%	946	6	19.35%	31	<0.001
New episode of atrial fibrillation	n (%)	246	26%	946	8	25.81%	31	0.85
Delirium	n (%)	129	13.64%	946	9	29.03%	31	0.03
Revision surgery (bleeding or tamponade)	n (%)	41	4.33%	946	6	19.35%	31	<0.001
Pacemaker implantation	n (%)	46	4.86%	946	1	3.22%	31	1.00
AKI	n (%)	210	22.2%	946	15	48.39%	31	0.001
RRT	n (%)	21	2.22%	946	4	12.9%	31	0.007
Pneumonia	n (%)	84	8.88%	946	9	29.03%	31	<0.001

AKI, Acute Kidney Injury; CABG, Coronary Artery Bypass Graft; CPB, CardioPulmonary Bypass; CVA, CerebroVascular Accident; ICU, Intensive Care Unit; PACU, Post Anesthesia Care Unit; RRT, Renal Replacement Therapy; TIA, Transient Ischemic Attack; P-value calculated with Mann-Whitney test for continuous variables and with chi-squared or fisher exact for categorical variables.

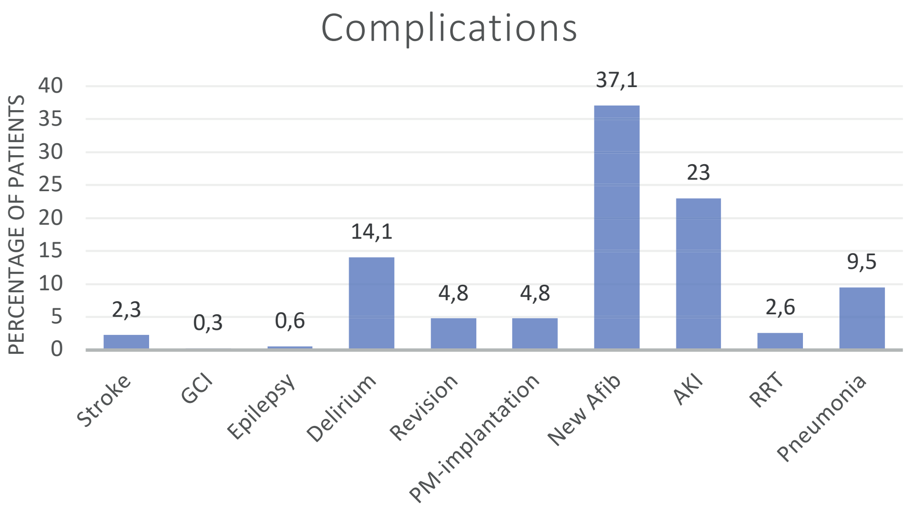

Fig. 2 — Incidence of post-operative complications during hospitalization after on-pump cardiac surgery.

Table II. — Significant risk factors for neurological complications and mortality, after cardiac on-pump surgery.

Outcome	Variables	Odds ratio	Confidence interval	P-value	Bonferonni corrected P-value
Combined neurological complications	Diabetes	2.34	1.08-5.06	*0.031*	0.53
	ICU stay	1.05	1.03-1.09	*<0.001*	*0.005*
	Readmission to ICU	3.95	1.12-13.85	*0.03*	0.54
	Hospital stay	1.03	1.02-1.05	*<0.001*	*<0.001*
Stroke	Endocarditis	2.83	0.93- 8.56	0.065	
Epilepsy	Preoperative A-fib	11.93	1.38-102.69	*0.024*	0.41
Mortality	Age	1.04	1.01-1.07	*0.020*	0.33
	AHT	2.64	1.20-5.81	*0.016*	0.27
	Diabetes	3.52	1.82-6.82	*<0.001*	*0.003*
	Preoperative A-fib	2.85	1.49-5.42	*0.001*	*0.02*
	Carotid stenosis	1.52	1.09-2.12	*0.014*	0.24
	Endocarditis	6.68	3.22-13.85	*<0.001*	*<0.001*
	CPB time	1.007	1.003-1.012	*0.001*	*0.02*
	Clamp time	1.009	1.001-1.018	*0.018*	0.34

2.64 (1.20-5.81), p=0.02), DM (OR 3.52 (1.81 – 6.82), p<0.001), A-fib (OR 2.84 (1.49-5.42), p=0.001), carotid stenosis (OR 1.52 (1.09-2.12), p=0.01), endocarditis (OR 6.68 (3.22-13.85), p<0.001), CPB time (1.007 (1.003-1.01), p=0.001), and clamp time (for the on-clamp subset, n=907) (OR 1.01 (1.001-1.02), p=0.02 (Table II). After Bonferroni correction, the following variables stayed significant: DM, A-fib, endocarditis, and CPB time.

Multivariable logistic regression for mortality

Remaining variables after backwards selection for multivariable logistic regression showed the following significant variables for mortality: carotid stenosis, CPB time, clamp time, DM, A-fib, and endocarditis. Lasso logistic regression for feature selection rendered the following variables: gender, DM, A-fib, endocarditis, cardioplegia, and clamp used (yes/no). Multivariable logistic regression was repeated for the coinciding variables of both methods of feature selection, which are available pre-operatively (i.e., DM, A-fib, endocarditis). From the resulting equation, the risk of postoperative mortality after on-pump cardiac surgery can be estimated based on the selected patient characteristics (Table III). Estimated risk ranges from a baseline risk of 1.46% when none of the selected risk factors are present, to 44.94% when all risk factors are present. The area under the ROC curve for the predictive model was 0.75.

Association of neurological complications and

mortality

A Chi-squared test of independence showed a significant association between neurological complications and mortality with p<0.001. Fisher's exact test confirmed this association for stroke (OR 7.23 (2.30-22.69), p=0.005) and GCI (OR 65.17 (5.74-739.38), p=0.003), but not for epilepsy (as no deaths were observed in any patient with a postoperative complication of epilepsy).

Risk factors for other complications

In exploratory analysis, univariate logistic regression was performed for the other postoperative complications displayed in figure 2. The following statistically significant associations were found: delirium was significantly correlated with age (OR 1.06 (95% CI 1.04-1.08), p<0.001), AHT (OR 1.96 (1.31-2.93), p<0.001), DM (OR 1.77 (1.16-2.71), p=0.01), history of A-fib (OR 2.16 (1.49-3.12), p<0.001), history of stroke (OR 1.82 (1.04-3.17), p=0.03), and cannulation site (i.e., peripheral as opposed to central) (OR 0.49 (0.29-0.83), p=0.01). The correlation remained significant after Bonferroni correction for age, AHT and history of A-fib.

Endocarditis was significantly associated with the risk of 3th degree AV-block, also after Bonferroni correction (OR 3.91 (1.85-8.26), p<0.001).

Discussion

In the present study, the overall incidence of neurological complications is comparable to other retrospective studies[3,6–8,17,18]. No statistically significant risk factors for postoperative neurological complications were found. The latter is possibly because of a low impact of these variables on outcome in our study and low incidence of these complications. It is possible that a subset of these preoperative factors would present as a significant risk factor, for example poorly controlled DM, but we did not specifically analyze that in this study. Of note, we specifically recorded the incidence of clinically overt stroke and epilepsy, and distinguished between stroke and global cerebral ischemia. In contrast, other studies often only focused on stroke or epilepsy[6,8,9,17,19–21].

Table III. — Predicted mortality risk based on selected preoperative variables modeled with multivariable logistic regression (AUC = 0.75).

Risk factors			Mortality Risk (%)
A-fib	DM	Endocarditis	
0	0	0	1.15
1	0	0	3.77
0	1	0	4.66
0	0	1	8.53
1	1	0	11.47
1	0	1	19.81
0	1	1	23.56
1	1	1	44.94

Stroke

The overall incidence of stroke in our study is 2.35%, which is comparable to that of earlier studies, with an incidence of 2 to 5%[3,6–8,17,18]. However, another study reported a high incidence of 17%[20]. There are important differences to note between these studies and ours:

We studied the incidence of clinically overt stroke in all elective on-pump procedures. Many other studies specifically looked at either CABG or valve surgery and included procedures both with and without CPB[2,3,6,7,9,22]. These studies showed a higher incidence of stroke for urgent surgery[6,19,23], and a lower incidence for procedures without CPB[6,22]. We excluded urgent procedures to remove the influence of a critical preoperative state and inability to assess the neurological status of the patient in advance. Furthermore, some studies do not register TIA[8,18], or included it as stroke[6,24], and some register it separately [3,20]. Because it is difficult in a postoperative setting to diagnose transient neurological symptoms retrospectively, we did not register the incidence of TIA.

We included all patients who experienced neurological symptoms with signs of ischemia on CT or MRI, patients who were diagnosed with stroke by a neurologist, and patients who suffered permanent postoperative neurological dysfunction. The diagnosis of stroke was based on radiological findings, compared to some other studies that only included patients with permanent neurological symptoms[8,25].

We also made a distinction with GCI, whereas other studies sometimes defined this as "stroke because of hypoperfusion"[9]. Should we include GCI in our recording of stroke, our incidence would rise to 2.66%. The strength of this study is that all patients who had a severe neurological complication, got a CT brain or MRI, which is important to confirm the diagnosis and distinguish between stroke and GCI.

Over time, the incidence of stroke will vary as well. Operative techniques and cardiopulmonary bypass have changed a lot, which could lead to a lower incidence of stroke. However, the surgical population has increased significantly in age and comorbidities, which could increase the incidence of stroke. The average age of our population was 68 years. In other comparable studies the average age was 65 years.

As shown in the prospective study of Messé et al. [20], we could miss a lot of subtle strokes when we do not routinely perform a complete neurological examination. Their study showed an incidence of clinical stroke in 17% of post-operative patients after standardized extensive neurological examination. They also found new ischemia on MRI in 50% of patients without neurological symptoms. Other studies show comparable incidences of silent stroke (around 40%)[26,27]. This "silent" ischemia can be visible on MRI of the brain. Patients in our study only got an MRI of the brain if they presented neurological symptoms and CT was negative. Therefore, our data is not significantly influenced by "silent ischemia". Although the relevance of silent ischemia is not clear, it might increase the risk of postoperative cognitive dysfunction[26,28].

Previous studies identified multiple risk factors for stroke after cardiac surgery, including DM, AHT, history of stroke, preoperative infection, urgent procedure, and long CPB time[3,6,8,9,19,23,29]. We did not find any statistically significant risk factors for stroke after on-pump cardiac surgery. This could be due to the low incidence of neurological complications and population size, requiring a larger study group to find small correlations. Risk facors could also be different because of a difference in studied population. With improved treatment of medical conditions over time, certain risk factors can become less significant in more recent studies. Excluding emergency procedures could also influence these risk factors.

Carotid stenosis was not associated with stroke in our population. This could be related to missing data since 25% of our patients did not have a preoperative evaluation of carotid stenosis. Other studies showed an increased risk of stroke for severe carotid stenosis[30]. Two patients in our study had a combined cardiac procedure with carotid endarterectomy. One of these patients had a postoperative embolic stroke, which could be due to an inherent risk of severe carotid stenosis or because of the combined procedure. However, a database analysis showed a comparable risk of in-hospital stroke in combined procedures compared to cardiac surgery alone[31].

Location of ischemia could be related to different etiological mechanisms. Stream jets by aortic cannula would cause more left sided infarction, while embolic particles from aortic manipulation (aortic clamp) would cause more right sided infarction[24].

We found a comparable amount of left sided (eight cases), right sided (seven cases) and bilateral stroke (eight cases). This does not suggest a specific causative mechanism. Most strokes were diagnosed as thrombo-embolic by neurologist and radiologist. Reducing the embolic load during cardiac surgery with CPB could be the best way to reduce neurological complications. Future strategies to reduce this embolic load should still be investigated. For TAVR specific "cerebral embolic protection devices" have been created, but these can't be used for open heart surgery[32]. Identifying patients with an increased risk for high embolic load, i.e. patients with more aortic atherosclerosis, with epiaortic ultrasound, could lead to modifications in surgical management. Different clamp techniques or "no touch technique" in these patients, could reduce the risk for postoperative stroke[33,34].

Global cerebral ischemia (GCI)

GCI is sometimes defined clinically as hypoxic-ischemic encephalopathy (HIE), or radiologically as global hypoxic ischemic injury[35,36].

In our subdivision of neurological complications, we defined global cerebral ischemia as a different entity according to the guidelines of the American Stroke Association. We made this distinction because we believe GCI should not just be included in the prevalence of stroke due to an important difference in etiology and implications. Stroke is caused by the obstruction of blood flow to a specific brain region, whereas GCI is caused by general hypoperfusion/hypoxia, as often seen after cardiac arrest and CPR[11]. This means GCI is caused by severe hemodynamic compromise, and is associated with a bad prognosis and increased mortality[36,37]. Cerebral ischemia could also be caused by a severe low flow state, but increasing general perfusion pressure did not reduce neurological complication in other studies[38]. All of our patients had a mean arterial pressure (MAP) of at least 50 mmHg on average while on CPB, which should be enough to prevent cerebral ischemia. Two out of three patients with GCI in our study, had an episode of severe hypoperfusion and had cardiopulmonary resuscitation (CPR)[36,37]. Since we excluded patients who died before extubation, our incidence of GCI is low. While stroke seems to be an operative complication which could possibly be prevented by interventions, GCI is a consequence of severe hemodynamic compromise and the most important intervention is to restore the hemodynamic state.

Epilepsy

The incidence of epilepsy in our study is only 0.61%, whereas in earlier studies this varied between less than 1 and 6%[39,40]. We assume our reported incidence is low for multiple reasons.

As we did not routinely perform EEG investigations, epileptic activity could have been missed. In the pilot study of Tschernatsch et al., 9% of patients showed epileptic signals after cardiac surgery[21]. Many patients stayed in our hospital only for a limited time and then continued their recovery in another hospital. Because seizures, in contrast to ischemic complications, often present later during hospitalization, this could influence our reported incidence.

Post-operative seizures are mainly caused by medication, metabolic factors and ischemia.

There is an important correlation between the severity of cerebral ischemia and the incidence of seizures[39,41]. If a postoperative seizure is associated with cerebral ischemia, there is a significant increase in postoperative morbidity and mortality. An isolated seizure without evidence for new ischemia does not seem to be related with worse outcome[42]. In our population, all patients with seizures fully recovered, except for one patient who was diagnosed with GCI on MRI.

Tranexamic acid (TXA) is one of the known pharmacological causes of seizures. The increased risk for seizures seems dose dependent. With doses of 50 to 100mg/kg, the risk of seizures is significant[39,40,43]. Smaller doses do not seem to increase the risk of seizures. We did not find a significant correlation between the use of TXA and seizures, possibly because relatively low doses of TXA were used. The dosages of TXA administered in our study population were usually around 10mg/kg loading dose, followed by a continuous infusion at 5 to 10mg/kg/h, or a loading dose of 30mg/kg without continuous infusion, according to protocol. We did not record the specific dose of TXA that was administered to each patient. However, in patients with seizures, we did specifically look at the dosage used, and found an unusually large dose in two patients; one patient received 100mg/kg TXA and the second patient got 60mg/kg.

Mortality

We found significant pre-operative risk factors for in-hospital mortality. A history of DM, A-fib and pre-operative endocarditis increased in-hospital post-operative mortality. DM and endocarditis are also identified as significant risk factors for mortality in the EuroSCORE II (a large prospective risk analysis model for mortality after cardiac surgery)[44]. A combination of these risk factors leads to a very high mortality risk in our study (Table III).

Longer CPB time was also related to a higher mortality. The latter may be due to more intraoperative complications prolonging surgery. These patients had a longer hospital stay and more complications. Stroke and GCI were significant post-operative risk factors for in-hospital mortality. If these factors could be prevented, we could improve survival. This highlights the importance of diagnosing and managing these complications early. Unfortunately, based on this study we can't suggest specific measures to reduce the incidence of stroke and GCI because we could not identify any significant risk factors. A future study could be indicated to look at potential other risk factors such as clamp technique, use of intraoperative cooling, or anticoagulation policy.

Study limitations

Being a retrospective study, we could only register complications if they were mentioned in the patient's file. Recording was based on clinical diagnosis during standardized patient care. However, we do not think that we missed a significant number of patients since severe neurological complications present with significant clinical signs, which are usually recorded immediately in patient's medical file. Because of the low incidence of neurological complications, our sample size might be too small to detect small correlations.

We excluded patients who died before neurological evaluation (n=8) because they could no longer be defined as having neurological complications before death. This could possibly influence our results since a neurological complication could lead to early death. The prevalence of risk factors was based on documentation in the preoperative file. If risk factors were not adequately documented in this file, they could have been missed.

It is important to note that we specifically looked at early postoperative complications during hospitalization. A lot of patients came to our facility for surgery and were transferred to their referring hospital for further recovery when they were clinically stable. Because stroke and GCI mostly occur in the early post-operative period[9], we believe this has no significant impact on the prevalence of the earlier mentioned complications. However, early hospital discharge could affect the prevalence of epilepsy. All neurological complications, except for one patient who presented with a late epileptic seizure, have been diagnosed during the first week.

Conclusion

The incidence of early neurological complications after elective on-pump cardiac surgery at our institution was comparable to those reported in earlier studies (overall incidence of 3.17%). No independent risk factors for these neurological complications were found. The occurrence of stroke and GCI significantly increased in-hospital mortality. This emphasizes the importance of these complications and early management of stroke. Strategies to reduce embolic load could significantly reduce the prevalence of neurological complications. Given the harmful effects of stroke, GCI and epilepsy on patient's outcome, we hope we can repeat the findings of the current study in a larger, well-designed prospective trial in adult cardiac surgery patients.

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