Impact of stroke on outcomes following cardiac surgery: Propensity matched analysis

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Abstract

Background Stroke remains a devastating complication of cardiac surgery. The aim of this study was to characterise the incidence of stroke and analyse the impact of stroke on patient outcomes and survival. Methods A retrospective analysis was performed of patients with a CT-confirmed stroke diagnosis between 01/01/2015 and 31/03/2019 at a single centre. 2:1 propensity matching was performed to identify a control population. Results Over the period 165 patients suffered a stroke (1.99%), with an incidence ranging 0.85% for CABG to 8.14% for aortic surgery. The mean age was 70.3 years and 58.8% were male. 18% had experienced a previous stroke or TIA. Compared to the comparison group, patients experiencing post-operative stroke had a significantly prolonged period of ICU admission (8.0 vs 1.1 days p<0.001) and hospital length of stay (12.94 vs 8.0 days p<0.001). Patient survival was also inferior. In-hospital mortality was almost 3 times as high (17.0% vs 5.9%; p<0.001). Longer-term survival was also inferior on Kaplan-Meier estimation (p<0.001). The 1-year and 3-year survival were 61.5% and 53.8% respectively compared to 89.4% and 86.1% for the comparison group. Conclusion Perioperative stroke is a devastating complication following cardiac surgery. Perioperative stroke is associated with significantly inferior outcomes in terms of both morbidity and mortality. Notably a 28% reduction in 1-year survival. The potential to reduce morbidity and mortality with the emergence of mechanical thrombectomy, demonstrates the need for clear links between cardiothoracic and stroke teams to support individuals affected by perioperative stroke.

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Perioperative stroke is a devastating complication following cardiac surgery. Perioperative stroke is associated with significantly inferior outcomes in terms of both morbidity and mortality. Notably a 28% reduction in 1-year survival. The potential to reduce morbidity and mortality with the emergence of mechanical thrombectomy, demonstrates the need for clear links between cardiothoracic and stroke teams to support individuals affected by perioperative stroke.

Key words: stroke, cerebrovascular accident, cardiac surgery, cardiopulmonary bypass, outcome

Introduction

Perioperative stroke is a devastating complication following cardiac surgery, with an incidence reported to be between 0.8% - 5.2%[1]. It is a cause of significant morbidity and mortality in the perioperative period, with associated financial impact due to prolonged hospital admission and ongoing rehabilitation requirements[2]. Perioperative stroke is diagnosed at two timepoints following cardiac surgery: on waking from anaesthesia or several days later and are believed to have different mechanisms. Early strokes, where patients are found to have neurological deficits or are slow to wake following cessation of sedation in the intensive care unit, are thought to be associated with embolism related to aortic and cardiac manipulation intraoperatively. Delayed strokes occurring following full recovery from anaesthesia are thought to be related to atrial fibrillation, cerebrovascular disease (carotid artery atherosclerosis or small vessel disease) or low output states[3].

A number of risk factors have been identified for the development of stroke following cardiac surgery and some have attempted to create models to quantify risk[2,4,5]. The challenge though is that many of these factors such as: age, diabetes, smoking history, chronic obstructive pulmonary disease and peripheral arterial disease are common to the development of cardiovascular disease and therefore the indication for cardiac surgery.

Over recent years, the population of patients undergoing cardiac surgery has changed: they are older and suffer more comorbidity and are having more complex surgery. The aim of this work was to evaluate the epidemiology and clinical impact of stroke in a contemporary population undergoing cardiac surgery at a high-volume centre.

Methods

Patient population

This was a retrospective observational study conducted at a single institution. This study was approved by the Royal Papworth Hospital Research and Development department and the requirement for patient consent waived. All patients undergoing adult cardiac surgery at Royal Papworth Hospital (United Kingdom) between January 2015 to April 2019 were included in this study. Demographic, intra-operative and post-operative outcome data, including return to theatre, mediastinal blood loss, blood product transfusion, and length of hospital and ICU stay was collected prospectively. Mortality information was obtained from the UK national patient administration system.

Perioperative management

All patients underwent surgery using cardiopulmonary bypass. Near infrared spectrometry is used selectively: in patients undergoing major surgeries and patients known to have carotid atherosclerosis to guide intraoperative management. Epi-aortic ultrasound is not available at our centre for assessing the ascending aorta prior to aortic instrumentation and cannulation. Patients confirmed to have suffered a stroke were discussed with our local stroke physicians for ongoing management advice.

Definitions

Stroke was defined on the basis of new changes on CT head scan indicating acute brain ischaemia or acute intraparenchymal haemorrhage AND consistent clinical findings suggesting acute stroke diagnosed by the local team. Acute Kidney Injury (AKI) grade was calculated using the Acute Kidney Injury Network classification[6].

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., San Diego, CA), and R 3.4.4 (R Core Team, Vienna, Austria). Propensity matching was performed to identify a two to one control population for the patients who experienced a stroke. This was performed using the 'nearest-neighbour' method whereby a control patient whose propensity score is closest to that of a patient returning to theatre is identified. Patients were matched on: age, sex, LV function, BMI, operation priority, operation category and logistic EuroSCORE. If multiple control patients have propensity scores that are equally close, one of these control subjects is selected at random. Standardised difference of means was calculated for both continuous and categorical variables in order to ensure that the frequency of a variable was equally balanced between the mini-bypass and matched populations.

The Kaplan-Meier method was used to plot the patient survival rates, with the log-rank (Mantel-Cox) test used to compare groups. Univariate analyses were performed. For comparison of groups, continuous variables were analysed with the Mann-Whitney U test if not normally distributed and with the Students t-test if normally distributed. Categorical variables were analysed with Fisher's exact test. $p < 0.05$ was considered statistically significant.

Results

Over the period of study, 8271 patients underwent adult cardiac surgery at our centre (excluding pulmonary endarterectomy and transplantation). Of these patients, 165 (1.99%) experienced a postoperative stroke. 77.0% were early, being detected on waking with presence of focal neurological signs or through not waking appropriately from sedation, and the remaining 23.0% were delayed, occurring after recovery from anaesthetic with later development of focal neurological signs.

The incidence of stroke varied significantly between the operation categories (Table 1), being most prevalent for aortic surgery (8.14%), and least prevalent for coronary artery bypass grafting (0.85%). In comparison, over the same period 2541 patients underwent thoracic surgical procedures with a stroke incidence of 0.2%. For aortic surgery, 55.7% of strokes occurred in patients operated emergently for acute type A aortic dissection. The median interval from operation to stroke confirmation on CT was 2.5 days. The most common type of stroke was ischaemic (93.4%), with intraparenchymal haemorrhage being much less common (6.6% each) (Table 2). For the patients surviving to discharge from our centre, the degree of disability was assessed using the Modified Rankin Scale (Table 3)

Demographics

The demographics of the patients experiencing a postoperative stroke are presented in Table 4. The mean age was 70.35 years and 58.8% were male. Only 43% of the patients experiencing a stroke underwent elective surgery. Risk factors for cerebrovascular vascular disease were prevalent: 8.5% had dialysis dependent renal failure, 26.7% had diabetes, 53.4% were current or ex-smokers and 17.3% had a history of peripheral vascular disease. A history of previous TIA or stroke was recorded in 18% of patients. The mean logistic EuroSCORE of patients experiencing a stroke was 17.49.

Propensity matched cohort

In order to contextualise outcomes for patients experiencing a postoperative stroke, propensity matching was utilised to identify a matched cohort of patients. Comparison of demographic parameters is presented in Table 3. On univariate analysis, there were some differences between the two groups. Patients experiencing stroke tended to have undergone more urgent or emergent procedures ($p<0.01$), had a higher preoperative creatinine level ($p=<0.01$), were in a higher NYHA class preoperatively ($p=0.01$) and were more likely to have had a previous TIA ($p=0.04$).

Clinical outcomes

Patients suffering a postoperative stroke had inferior outcomes compared to matched control patients (Table 5). Patients experiencing a stroke had a significantly prolonged period of ventilation (median 98 vs 10 hours; $p<0.001$) and length of ICU stay (median 192 vs 26.6 hours; $p<0.001$). Bleeding outcomes were similar between the patients with similar 12-hour blood loss ($p=0.325$) and return to theatre rate ($p=0.546$). The duration of inpatient stay was also significantly prolonged in patients experiencing a stroke (median 12.9 vs 8 days; $p<0.001$. The additional cost *per patient* attributed to the prolongation of ICU and ward LOS at our institution is £10,247. Furthermore, 59.4% of these patients were transferred to their local hospital for ongoing stroke rehabilitation incurring further costs to the healthcare system, compared to 12.2% for matched controls ($p<0.01$).

Patients experiencing a stroke had a high incidence of developing a respiratory tract infection (36.4% compared to 8.2% for matched controls) and 71.5% experienced acute kidney injury (stage 1 53.9%, stage 2 7.9% and stage 3 9.7%) compared to 20.8% for matched controls.

Survival

Patient survival was also inferior for patients experiencing a stroke compared to matched controls. In-hospital mortality was almost 3 times as high (17.0% vs 5.9%; $p<0.001$). Longer-term survival was also inferior on Kaplan-Meier estimation ($p<0.001$) (Figure 1). The 1-year and 3-year survival were 61.5% and 53.8% respectively compared to 89.4% and 86.1% for the matched patients. If 30-day conditional survival was imposed, there remained significantly inferior long-term survival ($p<0.001$) indicating the inferior survival does not entirely relate to early mortality following stroke (Figure 2).

Discussion

In this study we report an overall incidence of perioperative stroke of 1.99% in a large cohort of contemporary patients undergoing the breadth of adult cardiac surgery. A diagnosis of stroke had a significant impact on outcomes. Patients required prolonged hospital stays, experienced greater complications and experienced a 3-fold higher in-hospital mortality compared with matched controls. The 1-year survival was almost 28% lower.

The incidence of stroke varies significantly depending on the nature of the surgery, being most prevalent following major aortic surgery (8.14%) and lowest following isolated CABG (0.85%). The high prevalence following aortic surgery likely reflects the significant aortic manipulation that occurs and possible manipulation of the proximal carotid arteries leading to embolization of atherosclerotic material. It is also important to highlight that 55.7% of these patients had undergone emergency repair of type A aortic dissection. Other studies have also identified this association with aortic surgery[7], and they also note higher incidence following double procedures, presumably related to longer CPB times and greater likelihood of atherosclerotic embolisation. In some centres, epi-aortic scanning is performed to assess the ascending aorta prior to cannulation. This is not currently available at our centre but may facilitate reduced intraoperative embolisation. It is notable that the incidence of stroke following thoracic surgery at our centre over the same period was only 0.2%, highlighting that patients undergoing cardiac surgery are at a substantially greater risk, presumably related to factors specific to cardiac surgery and cardiopulmonary bypass.

In our series, over $\frac{3}{4}$ of the strokes were early, detected on waking from anaesthesia – likely reflecting an intraoperative event. In keeping with this, the vast majority of strokes were ischaemic. A meta-analysis reported almost equal incidence of early and delayed stroke across a large number of studies[2]. Many of the included studies were from the early 2000's and our lower proportion of delayed strokes – which are thought to be related to pre-existing cerebrovascular disease (chronic small vessel disease and carotid atherosclerosis) and atrial fibrillation[3], may reflect better pre-operative assessment and optimisation and improved anaesthetic management in the modern era leading to lower risk of stroke despite operating on higher risk patients[8].

As could be expected, risk factors for atherosclerotic disease were prevalent in our population of patients experiencing stroke including diabetes, smoking history, peripheral vascular disease and end stage renal impairment. We performed propensity matching in order to compare these patients to similar individuals undergoing similar procedures rather than comparing to the entire cohort as most other studies have. In terms of the atherosclerotic risk factors, there were no significant differences between those patients going on to experience a stroke, likely reflecting the similar pathophysiology for their cardiac disease and predisposition to stroke, making it challenging to use these factors to predict preoperatively patients at risk of developing stroke, although some have attempted to create risk scores. The relatively small number of patients in our study provided insufficient power to generate a scoring system from our data. The notable difference between the groups was that there was a significantly higher prevalence of previous TIA in the patients going on to experience a stroke. Interestingly, the authors of the meta-analysis discussed above, performed a meta-regression and identified previous neurological event as being the only factor significantly associated with development of perioperative stroke[2].

Carotid atherosclerosis is thought to be an important risk factor for perioperative stroke. However, there has been much debate on routine use of carotid doppler to diagnose significant carotid stenosis preoperatively, and this is not currently routinely used at our centre, although is used in selected cases. The prevalence of significant carotid stenosis in unselected patients is found to be low, and the incidence of stroke in patients with severe carotid stenosis is found to be too low to warrant widespread screening and is not recommended by current guidelines[9-12]. Some suggest selective screening (for example, patients >70 years with previous TIA/stroke) may be useful as there is some evidence that severe carotid stenosis is a significant predictor for perioperative stroke following cardiac surgery in these patients[13]. It is notable that even in studies describing preoperative carotid screening there is a low rate of carotid intervention even when severe stenoses are detected. The options include pre- or simultaneous carotid endarterectomy or carotid artery stenting. However, knowledge of carotid atherosclerosis is useful as it can lead to interventions to attempt to reduce the incidence of cerebrovascular ischemia, for example by ensuring high pressures and pulsatility whilst on

CPB.

The reason for interest in identifying patients at risk preoperatively is reinforced by examining patient outcomes following stroke. In our patients, there was significant prolongation of ICU and hospital length of stay and patients experienced much greater incidence of common complications including AKI and respiratory tract infections. The in-hospital mortality was 3-times higher than the matched controlled patients, at 17.0%, and significantly inferior longer-term survival was observed. It is worth emphasising that even when the significant early mortality is excluded, by imposing 30-day conditional survival, the survival of patients who suffered a stroke remains significantly inferior highlighting that the impact of stroke on mortality is not simply in the early phase but persists long-term. In addition to the financial burden placed on our institution, it is notable that 59.4% of these patients were transferred to their local hospital for ongoing stroke rehabilitation. It is also worth highlighting that the ICU and hospital stays refer to duration at our centre, and not the full inpatient stay which would be even greater considering the number being transferred. These outcomes are similar to other series reporting on patients following perioperative stroke. The 1- and 3-year survival rate from the meta-analysis were 80.2% and 73.0% respectively[2]. Our rates were significantly lower at 61.5% and 53.8%. We believe that this reflects the increase in older patients with more comorbidities undergoing cardiac surgery. Indeed, our matched cohort had survival rates of 89.4% and 86.1% which are significantly inferior to those presented in the meta-analysis of 99.5 and 99.2%.

The challenge of managing perioperative stroke has in part been due to the limited treatment options traditionally available, since thrombolysis is contraindicated in this population. There only option has been to administer high-dose anti-platelet medication and refer the patient for stroke rehabilitation. Recently though, mechanical thrombectomy has emerged as an important development in stroke management. Mechanical retrieval of thromboemboli from the cerebral arteries by neurointerventional radiology has been demonstrated to result in significantly greater neurological recovery in selected patients[14,15]. This is not contraindicated in surgical patients and there are now many reports of early postoperative patients undergoing mechanical thrombectomy with good clinical outcomes both in cardiac surgery and other surgical specialties[16-18]. Mechanical thrombectomy may offer cardiac surgical patients experiencing perioperative stroke an opportunity to achieve much greater neurological recovery than has been observed in the past.

Limitations

This is a single centre retrospective study which presents inherent limitations. We have used propensity matching which although a robust technique, has its limitations and it was notable that there were some differences between the two groups in baseline demographics. We have defined stroke on the basis of a combined clinical suspicion and evidence of changes on CT. It is possible that patients with an ischaemic infarct may be missed due to early imaging – however, if clinical suspicion remains it is our policy to reimage the patients after a few days therefore reducing the likelihood of significantly underestimating the incidence. In this series we relied on CT for diagnosing stroke, however it is known that sensitivity and specificity of MRI is greater. Due to small numbers we have not been able to use this study to characterise risk factors for the development of stroke or examine differences between early and late stroke. A significant proportion of patients were transferred to stroke rehabilitation centres and it has not been possible to obtain information of the duration of stay at these centres, to more completely report on inpatient duration.

Conclusion

Perioperative stroke is a devastating complication following cardiac surgery, with an overall incidence of approximately 2%. Unfortunately, the risk factors for stroke and cardiovascular disease significantly overlap which have hindered efforts to predict patients at elevated risk preoperatively. Perioperative stroke is associated with significantly inferior outcomes in terms of both morbidity and mortality, in particular a 28% reduction in 1-year survival. The potential to reduce morbidity and mortality with the emergence of mechanical thrombectomy, demonstrates the need for clear links between cardiothoracic and stroke teams to support individuals affected by perioperative stroke

The authors declare no conflicts of interest

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Author contributions: All authors conceived the study; JK, JA and NE collected and analysed the data. All authors contributed to writing and reviewing the manuscript. All authors approved the final version.

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Figure legend

Figure 1. Kaplan Meier survival estimate for patients suffering stroke following cardiac surgery compared with propensity matched control patients.

Figure 2. Kaplan Meier survival estimate for patients suffering stroke following cardiac surgery compared with propensity matched control patients, with 30-day conditional survival.

Tables

	Stroke (n=165)	**All patients (n=8106)**	**%**
Aorta surgery	61	749	8.14
CABG	27	3177	0.85
CABG + major cardiac	2	64	3.13
CABG + valve	30	1333	2.25
Major cardiac	1	98	1.02
Valve	44	2678	1.64

Table 1. Percentage of patients experiencing stroke over the study period. CABG – coronary artery bypass grafting. Major cardiac includes non-valve, non-CABG procedures, mostly pericardectomy, resection of atrial tumours and atrial septal defect closure.

Type of stroke

Type of stroke	**Frequency**
Cerebral infarction	155 (93.4%)
Intraparenchymal haemorrhage	10 (6.6%)

Table 2. Patients divided by type of stroke

Modified Rankin Score

Modified Rankin Scale	**Number of patients (%)**
0 – No symptoms	0 (0%)
1 – No significant disability	16 (11.7%)
2 – Slight disability	24 (17.5%)
3 – Moderate disability	47 (34.3%)
4 – Moderately severe disability	36 (26.3%)
5 – Severe disability	14 (10.2%)
6 - Dead	0 (0%)

Table 3. Assessment of the degree of disability as measured by the Modified Rankin Scale, for the 137 patients surviving to discharge from our centre.

	Stroke n = 165	Matched n = 330	Standardised difference	p-value
Age (mean (sd))	70.35 (10.52)	71.70 (11.29)	0.12	0.20
Sex = male (%)	97 (58.8)	204 (63.2)	0.09	0.40
BMI (mean (sd))	27.51 (5.07)	27.64 (4.79)	0.03	0.66
Priority (%) Elective Urgent Emergency	71 (43.0) 56 (33.9) 38 (23.1)	214 (66.3) 64 (19.8) 45 (13.9)	0.48	<0.01
Preoperative creatinine (mean (sd))	113.24 (71.36)	98.25 (64.91)	0.22	<0.01
Dialysis dependent (%)	14 (8.5)	23 (7.1)	0.26	0.06
Diabetes (%)	44 (26.7)	70 (21.7)	0.20	0.45
Smoker (%) Current smoker Ex-smoker Non-smoker Not recorded	12 (7.3) 76 (46.1) 69 (41.8) 8 (4.8)	17 (5.3) 141 (43.7) 141 (43.7) 24 (7.4)	0.14	0.56
COPD (%)	28 (17.0)	72 (22.3)	0.28	0.16
Peripheral vascular disease (%)	28 (17.3)	51 (16.0)	0.04	0.81
Previous TIA (%)	21 (13.0)	22 (6.9)	0.20	0.04
Previous stroke (%)	8 (5.0)	16 (5.0)	0.08	0.70
NYHA class (%) I II III IV Not recorded	29 (17.6) 59 (35.7) 54 (32.7) 17 (10.3) 6 (3.6)	48 (14.9) 136 (42.1) 103 (31.9) 10 (3.1) 26 (8.0)	0.37	0.01
Heart rhythm (%) Sinus Atrial fibrillation Other Not recorded	131 (79.1) 27 (16.4) 4 (2.4) 3 (1.8)	234 (72.4) 69 (21.4) 7 (2.2) 13 (4.0)	0.30	0.24
Left ventricular function (%) Good Moderate Poor	114 (69.1) 43 (26.1) 8 (4.8)	221 (68.4) 80 (24.8) 22 (6.8)	0.13	0.81
Surgery (%) Aorta surgery CABG CABG + major cardiac CABG + valve Major cardiac Valve	61 (37.0) 27 (16.4) 2 (1.2) 30 (18.2) 1 (0.6) 44 (26.7)	105 (32.5) 52 (16.1) 5 (1.5) 69 (21.4) 2 (0.6) 90 (27.9)	0.11	0.93
EuroSCORE (mean (sd))	8.86 (3.13)	8.44 (3.99)	0.12	0.78
Logistic EuroSCORE (mean (sd))	17.49 (14.75)	17.54 (19.78)	<0.01	0.89
Bypass time (mean (sd))	152.09 (89.13)	118.10 (69.59)	0.43	<0.01

	Stroke n = 165	**Matched n = 330**	**Standardised difference**	**p-value**
Cross-clamp time (mean (sd))	82.33 (44.51)	74.63 (35.52)	0.19	0.12

Table 4. Comparison of patient demographics. Patients were propensity matched on age, sex, left ventricular function, BMI, operation priority, operation category and logistic EuroSCORE. BMI – body mass index; CABG – coronary artery bypass grafting; COPD – chronic obstructive pulmonary disease; TIA – transient ischaemic attack

	Stroke n = 165	**Matched n = 330**	**P value**
Hours of ventilation (median (range))[a]	98.00 [34.75, 177.75]	10.00 [6.00, 19.00]	**<0.001**
12-hour blood loss (mean (range) ml) [a]	300.00 [175.00, 525.00]	275.00 [175.00, 450.00]	0.325
ICU length of stay (median (range) hours) [a]	191.97 [107.48, 314.93]	26.59 [21.53, 93.70]	**<0.001**
Hospital length of stay (median (range) days) [a]	12.94 [8.10, 18.00]	8.00 [6.00, 11.89]	**<0.001**
In-hospital mortality (%)[b]	28 (17.0)	19 (5.9)	**<0.001**

Table 5. Post-operative outcomes. Statistical analysis:[a] – Mann-Whitney U test, [b] – Fishers exact chi squared test. ICU – intensive care unit

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