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Predictors of cerebrovascular events in patients subjected to isolated coronary surgery. The importance of aortic cross-clamping☆

Pedro E. Antunes, J. Ferrão de Oliveira, Manuel J. Antunes*

Department of Cardiothoracic Surgery, University Hospital, 3049 Coimbra Codex, Portugal

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Abstract

Objective: Stroke is a major complication after coronary surgery, occurring in 1–4% of the patients. In this study, we evaluate the incidence and pre- and intraoperative risk factors for the development of a cerebrovascular accident (CVA) and the impact of such an event on perioperative mortality and on hospital length of stay. **Methods**: Data from 4567 patients submitted to isolated coronary artery bypass grafting (CABG) with hypothermic ventricular fibrillation between 1992 and 2001 were entered prospectively into a dedicated computerized database and analyzed retrospectively at this time. Univariate and multivariate analyses were performed where appropriate. **Results**: The incidence of postoperative CVA was 2.5% (116 patients). Multivariable logistic regression identified the following variables to be independent predictors of a postoperative CVA: cerebrovascular disease ($P < 0.001$; odds ratio (OR), 2.66), peripheral vascular disease ($P < 0.001$; OR, 2.33), number of periods of aortic cross-clamping ($P = 0.019$; OR, 1.31 per each period of aortic cross-clamping), LV dysfunction ($P = 0.012$; OR, 1.82) and age ($P = 0.008$; OR, 1.28 per each 10 years). Non-elective surgery showed a marginal significance ($P = 0.08$; OR 1.83). The 30-day mortality for patients who experienced a CVA was 16.4% versus 0.6% for patients who did not ($P < 0.001$). Postoperative CVA increased the length of hospital stay threefold to 20.3 ± 28.3 days as compared with patients who did not have a postoperative CVA (7.6 ± 4.2 days; $P < 0.001$). **Conclusions**: Postoperative CVA dramatically increases the mortality and length of stay after CABG. Identification of predisposing factors permits preoperative risk stratification and may facilitate improved patient selection or optimization. Our study adds evidence to the superiority of the fibrillation technique over intermittent cross-clamping of the aorta, among non-cardioplegic techniques, in terms of neurological protection.

Keywords: Stroke; Risk factors; Coronary bypass surgery

1. Introduction

The incidence of stroke during or immediately after coronary artery surgery (coronary artery bypass surgery; CABG) is reported to be between 1% and 4% [1–9]. Next to the operative mortality, stroke is the most dreaded complication following CABG, not only for the devastating consequences to the patient and family, but also for the vastly increased cost of hospitalization and subsequent care. Additionally, it partially offsets the benefits of CABG over other forms of treatment, i.e. medical therapy and percutaneous revascularization procedures.

We evaluated the risk factors for a postoperative cerebrovascular accident (CVA) among 4567 patients submitted to isolated CABG during a 10-year period (1992–2001). Although there are numerous reports on postoperative stroke after CABG, most are based on series that routinely use aortic cross-clamping and cardioplegia for myocardial protection. Our study specifically addresses this subject on a patient population where coronary revascularization was performed under ventricular fibrillation with or without periods of aortic cross-clamping, a technique increasingly used by surgeons throughout the world. We also recognized an opportunity to study the importance of cross-clamping the aorta because, unlike other series, we had patients who had and patients who did not have cross-clamping of the aorta. Our objective was: (1) to determine the incidence of a CVA after CABG performed under fibrillatory arrest; (2) to identify preoperative and intraoperative factors associated with the occurrence of CVA, with particular emphasis on the importance of not cross-clamping the aorta; and (3) to evaluate the impact of a CVA on perioperative mortality and on hospital length of stay.

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* Corresponding author. Tel.: +351-239-400418; fax: +351-239-829674.
E-mail address: antunes.cct.huc@mail.telepac.pt (M.J. Antunes).

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Table 1
Univariate analysis of risk factors in patients with and without a CVA[a]

Risk factors[b]	CVA ($n = 116$)	Non-CVA ($n = 4451$)	P-value
Age (years)	63.40 ± 8.0	60.60 ± 9.3	< 0.001
Body surface area (cm^2)	174.33 ± 16.85	178.01 ± 14.01	0.021
Body mass index	25.73 ± 2.26	26.08 ± 2.31	0.105
Female sex	18.97	11.57	0.015
Diabetes mellitus	31.90	22.31	0.015
Hypertension	68.97	56.70	0.008
Dyslipidemia	55.17	58.75	0.440
Recent smoking	12.07	11.48	0.845
PVD	25.0	9.89	< 0.001
CVD	16.38	4.92	< 0.001
Previous carotid surgery	2.59	2.25	0.808
Anemia	4.31	3.91	0.826
COPD	6.90	3.23	0.030
Cardiomegaly	16.38	11.48	0.104
Recent AMI (<30 days)	7.76	5.03	0.188
Unstable angina	6.90	6.81	0.970
Angina CCS class III or IV	51.72	39.70	0.009
Cardiac reoperation	2.59	1.66	0.446
Left main disease	18.96	16.45	0.471
Non-elective surgery	12.93	6.47	0.006
LV dysfunction (EF < 0.4)	23.28	13.01	0.001
Three-vessel disease	81.03	75.20	0.150
No. of grafts (mean/patient)	2.93 ± 0.87	2.80 ± 0.81	0.102
Coronary endarterectomy	9.48	7.03	0.310
No. of cross-clamps (mean/patient)	0.44 ± 0.95	0.25 ± 0.63	0.036
Mean CPB time (min)	65.47 ± 23.70	62.29 ± 23.34	0.157

[a] CVA, cerebrovascular accident; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PVD, peripheral vascular disease; LV, left ventricle; EF, ejection fraction; CPB, cardiopulmonary bypass.
[b] Unless otherwise specified, variables are expressed as %.

2. Patients and methods

2.1. Patient population and risk factors

A consecutive series of 4567 patients undergoing CABG at our institution from January 1992 through December 2001 was evaluated. Only patients who underwent isolated coronary revascularization were included in this study. There were 4030 men (88.2%) and 537 women (11.8%), and the mean age was 60.6 ± 9.2 years (median 62 years).

The primary outcome event in this study was an in-hospital perioperative or postoperative cerebrovascular accident, classified as either a transient ischemic attack (TIA) or a stroke. A TIA was defined as a focal cerebral dysfunction of presumed vascular origin that resolved completely within 24 h. A stroke was defined as a focal or global cerebral dysfunction of presumed vascular origin lasting more than 24 h. In patients with a previous history of stroke, a new cerebrovascular event was diagnosed if new neurologic findings or prolonged worsening of their pre-existing neurologic deficits were observed. The diagnosis was made by members of the surgical team, who saw all patients during daily visits, and confirmed by a neurologist and/or appropriate brain imaging. For the statistical analysis of cerebrovascular accidents, patients were categorized into two groups: CVA (including stroke and TIA) and non-CVA.

Preoperative demographic and clinical data, and perioperative and in-hospital outcome data were collected prospectively and entered into a dedicated computerized database. From this database, a total of 26 preoperative and perioperative variables believed to be potentially relevant to the occurrence of a CVA were analyzed (Table 1).

2.2. Surgical technique for CABG

Cardiopulmonary bypass was conducted with nonpulsatile flow and mild hypothermia (32 °C) and the systemic perfusion pressure was electively maintained at 55–65 mmHg. A left ventricular vent was always introduced through the right superior pulmonary vein and the left atrium. No topical cooling was used.

All operations were performed under hypothermic ventricular fibrillation without cardioplegia. This method was described in detail in previous reports [10,11]. Control of the residual and/or collateral blood flow was achieved by a variety of methods. Most commonly, we could obtain a relatively dry field with the use of the coronary occluders and a soft jet of oxygen. Hence, in the majority (81.9%) of

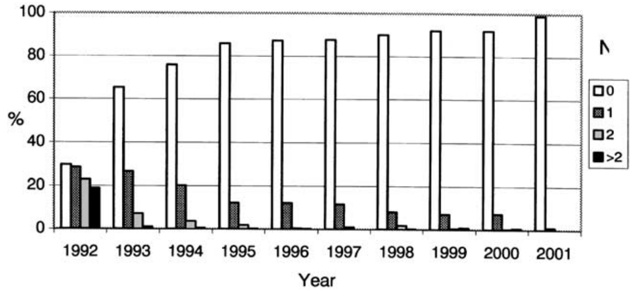

Fig. 1. Percentage of patients submitted to isolated CABG without and with periods of aortic cross-clamping (N), per year.

the patients the aorta was not cross-clamped at any time. In the remaining patients, the aorta was cross-clamped at least once (mean time per period of cross-clamp: 5.2 min), mostly in the first years of this series, with the only purpose of obtaining a drier field for a better exposure of anastomoses and/or endarterectomy site. In recent years, aortic cross-clamping was avoided whenever possible (Fig. 1).

Usually, all distal anastomoses were constructed first, followed by all proximal anastomoses during a single partial clamping period after the heart was defibrillated and allowed to beat. When important atherosclerotic disease of the ascending aorta was present, as assessed by visual inspection and palpation of the site of proximal vein graft anastomoses, aortic clamping was not used and the proximal anastomoses were performed as an open method during short periods of very low pump flow. We are happy with this method, although it obliges special precautions to prevent air from entering the systemic circulation. Also, to avoid cerebral damage from excessive time of low flow, we strictly keep these periods at no longer than 2–3 min.

A bloodless prime was used in more than 95% of the cases, whenever the preoperative hematocrit was greater than 35%, and blood was not administered unless that parameter fell bellow 20–22% during cardiopulmonary bypass. Collected mediastinal blood shed during the first 6 postoperative hours was reinfused. Homologous blood transfusion was required in less than 10% of the patients.

2.3. Statistical analysis

Univariate analysis of categorical data was carried out by χ^2 analysis (2×2 contingency tables) or the Fisher's exact test. Univariate analysis of continuous variables was carried out using the unpaired *t*- test. Any variable that achieved a *P*-value of 0.1 or less in the univariate analysis was subjected to a multiple logistic regression analysis. In the final model, a factor associated with a *P*-value of less than 0.05 was considered as an independent risk factor associated with the event. The odds ratio (OR) and 95% confidence interval (CI) for each independent variable in the final regression model are presented. The final multivariable logistic regression was used to predict the probability of CVA using the following equation:

$$\pi = e^{(\beta 0+\beta 1\times 1+\beta 2\times 2+\ldots+\beta i\times i)}/1 + e^{(\beta 0+\beta 1\times 1+\beta 2\times 2+\ldots+\beta i\times i)}$$

where π is the probability of CVA; β_0 is a constant; β_1, $\beta_2,\ldots,\beta_i$ are regression coefficients; and $x_1, x_2,\ldots,x_i$ are variables in the equation. All data were analyzed with the assistance of the Systat statistical software.

3. Results

One hundred and sixteen neurologic events occurred in the 4567 patients (2.5%) submitted to isolated CABG during the study period. The data of the univariate analysis of the risk factors that influenced the development of a CVA are shown in Table 1. The following reached statistical significance ($P < 0.05$): increasing age, female sex, lower body surface, diabetes mellitus, hypertension, peripheral vascular disease, cerebrovascular disease, angina CCS class III or IV, chronic obstructive pulmonary disease (COPD), non-elective surgery, left ventricular dysfunction (ejection fraction (EF) < 0.4) and the number of periods of aortic cross-clamping. Multiple logistic regression analysis identified the following risk factors to be independently significant for development of a postoperative stroke (Table 2): increased age, peripheral vascular disease, cerebrovascular disease, left ventricular dysfunction, and the number of periods of cross-clamping. In addition, non-elective surgery approximated significance as a risk factor ($P = 0.08$).

The influence of the various risk factors in the postoperative CVA rate is demonstrated in Table 3. Of notice is the influence of the number of periods of aortic cross-clamping with associated risk factors. For instance, in a 60-year-old

Table 2
Multiple logistic analyses of risk factors for stroke after coronary artery bypass grafting (CABG)

Risk factor	Variable estimate	Standard error	*P*-value	Odds ratio	95% CI
Cerebrovascular disease	0.978	0.277	< 0.001	2.660	1.55–4.56
Peripheral vascular disease	0.803	0.233	0.001	2.231	1.41–3.52
LV dysfunction (EF < 0.4)	0.601	0.239	0.012	1.825	1.14–2.91
Age	0.031	0.012	0.008	1.283[a]	1.03–1.60
No. of aortic cross-clamps	0.268	0.114	0.019	1.308[b]	1.05–1.63
Constant	− 6.049	0.737	< 0.001		

[a] For each 10 years of age.
[b] For each period of aortic cross clamp.

Table 3
Predicted risk of postoperative stroke in patients with 60 years submitted to isolated CABG (see text for explanation)

Risk factor present			Predicted risk (%) No. of aortic cross-clamps			
CVD	PVD	LV dysfunction (EF < 0.4)	0	1	2	3
−	−	−	1.5	1.9	2.5	3.3
−	−	+	2.7	3.5	4.5	5.8
−	+	−	3.3	4.2	5.5	7.0
+	−	−	3.9	5.0	6.5	8.3
−	+	+	5.8	7.5	9.5	12.1
+	+	−	8.3	10.5	13.3	16.7
+	+	+	14.1	17.7	21.9	26.8

patient, if no other significant risk factors were present, the predicted risk of a postoperative CVA was 1.5% if there was no aortic cross-clamping and 3.3% if there were three periods of cross-clamping. For patients in whom all significant factors were present, the risk of CVA was 14.1 and 26.8%, respectively.

The perioperative mortality was 16.4% in patients who experienced a CVA as compared to 0.6% in patients who did not develop a CVA ($P < 0.001$), and 43.2% of all perioperative deaths occurred in patients who had such an event. The occurrence of a CVA increased the length of hospital stay almost threefold to 20.3 ± 28.3 days, by comparison with patients who did not develop a CVA (7.6 ± 4.2 days; $P < 0.001$).

4. Discussion

Stroke is a devastating complication that increases mortality, morbidity, hospital stay and cost. The reported incidence of stroke associated with coronary artery surgery varied widely, depending on the definition and accuracy of diagnosis, between 1 and 4% [1–9]. In our population, analyzed prospectively for the occurrence of complications of CABG, the incidence was 2.5%, including episodes of TIA. Patients who had a CVA had a perioperative mortality of 16.4% and a mean hospitalization of 20.3 days, compared with 0.6% mortality and a mean hospitalization of 7.6 days for the non-CVA patients. Similar results have been reported by others and did not change during the past decade.

Identification of risk factors allows preoperative risk stratification and may facilitate improved patient selection. Additionally, this information may contribute to reduce the risk of a stroke by providing an opportunity for adequate medical and surgical intervention. Although many reports on postoperative stroke after CABG have been published, our study specifically addresses this subject in a patient population where coronary revascularization was performed under ventricular fibrillation with or without periods of aortic cross-clamping, techniques which have an increasing number of supporters.

Using multiple logistic regression analysis, we have identified four preoperative and one intraoperative risk factors independently associated with the development of a postoperative stroke: increasing age, cerebrovascular disease, peripheral vascular disease, left ventricular dysfunction (EF < 0.4) and the number of periods of aortic cross-clamping. Additionally, non-elective surgery approximated significance as an independent risk factor.

In most reported series, advancing age has been identified as an important predictor of perioperative stroke [1–9]. Given the higher prevalence of systemic atherosclerosis, cerebrovascular disease and underlying cognitive dysfunction, elderly patients are at increased risk of cerebral injury. Our data confirm the same trend of higher stroke rate in older patients. The mean age of our patients without CVA was 60.6 years and 63.4 for patients who developed a CVA. The odds ratio for developing a CVA was 1.3 for each additional decade of life.

A history of prior stroke or ITA is a strong predictor of recurrent stroke, and this variable it is present in the great majority of the risk models [1,3–9]. Such a history denotes the existence of pathologic conditions within the cerebrovascular system. In the present series, history of prior stroke or ITA (patients classified as having cerebrovascular disease) was the strongest predictor, with an odds ratio of 2.7. The incidence of a new CVA in this group of patients was 8.0%, versus 2.2% in patients without prior history of stroke or ITA.

Peripheral vascular disease and left ventricular dysfunction where also identified in this study as significant risk factors for CVA. Several other studies have identified the same risk factors for stroke during CABG [2,3,5,9]. Most probably, the mechanism related to the higher rate of CVA in patients with LV dysfunction observed in this series is related to the increased incidence of left side intracardiac thrombus and the use of left ventricular venting. Possibly, these patients should undergo routine preoperative assessment for the presence of intracardiac thrombus, in which case ventricular venting should, obviously, not be used.

Other risk factors that have been reported by others, including history of pulmonary disease [7], prolonged cardiopulmonary bypass time [5,6,8], unstable angina [7], reoperation [7], hypertension [6,8,9], diabetes mellitus [3,5,7–9], and recent smoking [5], were not independently related to stroke in our study.

4.1. Association between cross-clamping the aorta and cerebrovascular events.

The majority of strokes that occur during coronary surgery are caused by cerebral macroemboli. This etiology is supported by several studies that show that the great majority of the cerebral lesions are ischemic and localized

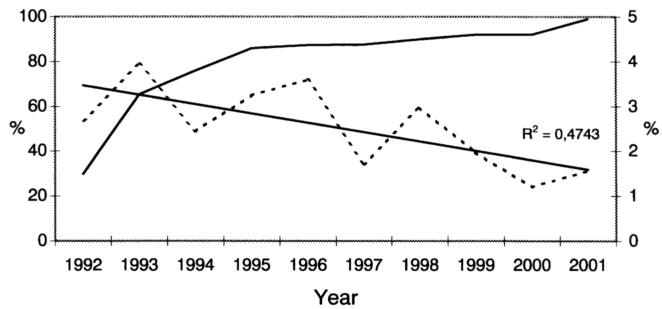

Fig. 2. Inverse relationship observed between the performance of surgery without aortic cross-clamping and the incidence of CVA over time (dashed line).

in the territory of major cerebral arteries [3,12]. Involvement of the middle cerebral artery is also a common finding.

There is a consensus that the principal source of cerebral macroemboli is the ascending aorta. By potentially reducing the embolic consequences of manipulation of the aorta, fibrillatory arrest without aortic cross-clamping may decrease the incidence of cerebrovascular accidents in coronary artery bypass grafting. Experimental evidence for the superiority of this technique includes pathological demonstration of aortic damage following clamp application and echo-Doppler documentation of cerebral artery emboli following the application and removal of aortic clamps [13]. However, this theoretical advantage has not been conclusively demonstrated. We had the opportunity to more carefully evaluate the importance of cross-clamping the aorta, because we had patients who had aortic occlusion and patients who did not, and found that the number of periods of aortic cross-clamping was an independent risk variable for CVA (odds ratio of 1.3 per each period of cross-clamping).

To our knowledge, this is the first report that specifically addresses this variable, quantifying the risk associated with each period of aortic cross-clamping. This is somewhat in contrast with the series reported by Musumeci et al. [14], who found comparable incidences of postoperative neuropsychological disturbances with single-clamping technique versus intermittent cross-clamping, although their study only included patients with no clinical evidence of aortic or cerebrovascular disease. The conclusion of our study adds evidence to the superiority of the fibrillation technique over intermittent cross-clamping of the aorta, among non-cardioplegic techniques, in terms of neurological protection. Because of our early awareness of this fact, we have progressively reduced the number of periods of cross-clamping, which are now consistently avoided in more than 90% of the patients. This is, probably, one of the causes of the decreasing incidence of CVA over time (Fig. 2). Although this technique reduces the amount of aortic manipulation, there was always aortic cannulation and almost always the use of a side-biting clamp to performed the proximal anastomoses. Calafiore et al. [16] have recently reported the influence of these aortic manipulations on the incidence of cerebrovascular accidents. These authors concluded that cardiopulmonary bypass (CPB), per se, was not a risk factor for higher CVA incidence, and use of side-clamping provides the same CVA risk as in patients in whom CPB, aortic cannulation, and cross-clamping were used.

Although the majority of strokes that occur during coronary surgery are caused by cerebral macroemboli, we cannot underestimate the importance of microemboli. There is some reported evidence [15] that shed blood returned to the patient can increase the probability of neurological insult due to increased lipid microemboli cerebral phenomena. In our group study, collected mediastinal blood shed was reinfused during the first 6 postoperative hours, and this may have contributed to an increased incidence of neurological damage.

We have studied an unselected cohort of CABG patients that enabled the documentation of 116 cerebrovascular events and allowed the creation of a statistically powerful regression model to identify pre and intraoperative predictors of CVA in patients subjected to isolated coronary surgery. However, the present study has limitations that include those inherent to any retrospective analysis, even when data were colleted prospectively, as was the case. Although evaluation by independent neurologist and/or brain imaging was routinely performed in patients with suspected neurological events, there was no neuropsychological testing that would have enabled the assessment of more subtle changes in mental performance and behavior. The clinically obvious CVA, the outcome measure in this study, likely represents only the tip of the iceberg. Another weakness of our study is related to the method used for detection of significant ascending aortic disease. In this group of patients, the presence of atherosclerotic plaque in the ascending aorta was assessed by visual inspection and palpation, although this method has been proved to be unreliable [17]. Epiaortic ultrasonography is now the more accurate method of assessing atherosclerosis of the ascending aorta and can be used to guide surgeons not only to more accurately decide when it is unsafe to clamp the aorta but also to instrument those areas of the aorta that are relatively disease-free.

In summary, CVA that occurred in 2.5% of the 4567 patients subjected to isolated CABG, proved to be a devastating complication, carrying a mortality of 16.4%. Four preoperative risk factors for stroke were identified: age, cerebrovascular disease, peripheral vascular disease and left ventricular dysfunction. Additionally, we have also identified cross-clamping and the number of periods of aortic cross-clamping as independent risk factors for CVA. Hence, we believe that fibrillatory arrest is superior to intermittent cross-clamping, among non-cardioplegics techniques. Identification of the risk factors for stroke may constitute valuable information for preoperative risk stratification and to facilitate patient selection or optimization. Indeed, prior knowledge of these factors resulted in a decreasing rate of cerebrovascular events in our experience.

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Appendix A. Conference discussion

Dr O. Alfieri (*Milan, Italy*): Do you suggest an echo Doppler study of the carotids in all patients submitted to coronary surgery?

Dr Antunes: Yes. Nevertheless, we do it mainly in four groups of patients: old patients, patients with peripheral and vascular disease, patients with history of stroke and TIA, and patients with a carotid bruit. We do not do it routinely.

Dr J. Tsai (*Pingtung, Taiwan*): What predictors or indicators are you using to predict CVA during your CABG surgery: one, carotid artery Doppler examination; two, epiaortic cardiac 2-D echo; three, 24-h Holter monitor? It is not just saying that smoking, old age, cross-clamping time, et cetera. All of these are not good for the cardiac surgeon at all.

Dr Antunes: Certainly the epiaortic echo is the gold standard for analyzing the ascending aorta in terms of atherosclerotic disease, but we don't have such an instrument at our institution.