ORIGINAL ARTICLE

Braz J Cardiovasc Surg 2006; 21(2): 173-179

Predictors of major neurologic dysfunction after coronary bypass surgery

Preditores de disfunção neurológica maior após cirurgia de revascularização miocárdica isolada

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RBCCV 44205-813

Abstract

Introduction: **Patients who undergo myocardial revascularization procedures (CABG) are prone to neurologic dysfunction. Significant neurologic problems implicate a higher mortality rate and permanent functional deficiencies.**

Objective: **The aim of this study was to evaluate the incidence and to identify possible predictors of major postoperative neurologic dysfunction (defined as stroke) and to evaluate early clinical outcomes in a non-selected cohort.**

Method: **A total of 1760 consecutive patients, who underwent CABG in isolation in the San Lucas Hospital - PUCRS between January 1997 and February 2004, were enrolled. Demographic and laboratory data, information regarding the procedure and perioperative endpoints were collected prospectively using a standard protocol data register of the postoperative heart unit in our hospital. Variables with a p-value of no greater than 0.05 given a confidence interval of 95% were considered statistically significant.**

Results: **In this study, 52 (3%) patients presented with major neurologic dysfunction. In the univariable analysis advanced age, higher prevalence of obstructive pulmonary disease, prior cerebrovascular disease, high mean fibrinogen levels, the occurrence of shock or severe hypotension, presence of supraventricular tachycardia (atrial fibrillation or flutter), occurrence of systemic inflammatory syndrome and prolonged mechanical ventilation were associated with stroke. In the multivariable analysis prior history of cerebrovascular disease and obstructive pulmonary disease**

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Article received in July, 2005
Article accepted in May,2006

presented as independent predictors for the occurrence of major neurologic dysfunction. Prolonged mechanical ventilation was also independently associated with this complication. Furthermore, the occurrence of stroke significantly increased the duration of hospital stay and in-hospital mortality.

Conclusion: **Neurological dysfunction is still a significant cause of morbidity after CABG.**

Descriptors: **Cerebrovascular accident. Cerebrovascular disorders. Cardiac surgical procedures, adverse effects. Myocardial revascularization.**

Resumo

Objetivo: **Avaliar a incidência e os fatores preditores de disfunção neurológica maior pós-operatória e a evolução clínica precoce em uma coorte não selecionada.**

Método**: Um total de 1760 pacientes consecutivos submetidos a CRM isolada, no Hospital São Lucas da PUCRS, entre janeiro de 1997 e fevereiro de 2004, foram incluídos. Dados demográficos, informações do procedimento e desfechos perioperatórios foram coletados usando-se o protocolo do registro de dados da Unidade de Pós-Operatório de Cirurgia Cardíaca do nosso hospital. As variáveis consideradas estatisticamente significativas foram aquelas com p <0,05 e intervalo de confiança de 95%.**

Resultados: **Na nossa amostra, 52 (3%) pacientes evoluíram com disfunção neurológica maior (AVC). Na análise univariada, idade avançada, maior prevalência de doença pulmonar obstrutiva crônica (DPOC), doença cerebrovascular (DCV) prévia, média de fibrinogênio elevada, desenvolvimento de choque ou hipotensão grave, presença de taquicardia supraventricular (fibrilação atrial ou *flutter*), ocorrência de síndrome da resposta inflamatória sistêmica (SIRS) e ventilação mecânica prolongada estiveram associados ao desenvolvimento de AVC. Na análise multivariada, a história prévia de DCV e DPOC demonstraram ser preditores independentes para a ocorrência de disfunção neurológica maior. Ventilação mecânica prolongada também apresentou associação independente com o desfecho. Além disso, a ocorrência de AVC aumentou significativamente o tempo de internação hospitalar e a mortalidade intra-hospitalar.**

Conclusão: **A disfunção neurológica permanece sendo relevante causa de morbidade hospitalar, no pós-operatório de CRM com circulação extracorpórea.**

Descritores: **Acidente cerebrovascular. Transtornos cerebrovasculares. Procedimentos cirúrgicos cardíacos. Cirurgia cardíaca, efeitos adversos. Revascularização miocárdica.**

INTRODUCTION

Patients submitted to coronary artery bypass grafting procedures (CABG) are particularly susceptible to neurological dysfunction in the postoperative period. Significant neurological problems can occur after heart surgery, implicating in high mortality rates with survivors frequently acquiring permanent functional deficiencies.

However, despite of neurological complications being responsible for high morbimortality, their incidence varies greatly in publications, mainly due to differences in definitions, the homogeneity of the populations in the study and the length of follow up. Published studies are generally performed at one center and involve a small number of patients. Thus, the incidences of perioperative ischemic brain events and neuropsychological dysfunction reported in the literature have variations of 0.4% to 5.4% and 25% to 79% respectively [1-5].

In spite of improvements in the results of CABG over the last few years, with a reduction in the incidence of complications, including mortality, the rate of perioperative cerebrovascular events seems to have remained unchanged. Advances in myocardial protection strategies and refinements in the surgical and anesthetic techniques have enabled the extension of the benefits of heart surgery to older patients giving satisfactory results over both short and long terms. Thus, the profile of patients submitted to CABG has changed mainly in respect to the increases in ages and associated comorbidities, a situation that has made neurological complications related to the procedure of particular concern.

The National Cardiac Database of the Thoracic Surgery Society reported an incidence of new neurological events (stroke, transitory stroke or coma lasting for more that 24 hours) of 3.3% in a study of more than 400,000 patients [6]. This incidence increases according to the complexity of the surgery and the mortality at 30 days was significantly higher in patients suffering new neurological events compared to a control group (30% versus 4%).

The most common permanent neurological complication is stroke, but reversible ischemic deficits, encephalopathy, coma, cognitive deficits and convulsions can occur. Two distinct presentations have been described in the literature: Type I (local lesion, stupor or coma), which is considered stroke and Type II (deterioration of the intellectual function, memory defects or convulsions) which are changes in the cognitive and intellectual function.

Strokes are severe and debilitating complications associated with a reduction in the quality of life and increased mortality. The presence of neurological sequels significantly increases the probability of prolonged hospitalization and the necessity of additional care with a great economic impact on the healthcare system.

The incidence of strokes related to heart surgery vary from 0.4 to 14% in different studies depending mainly on the target population and on the specific procedure to which the patient is submitted [1,7-9].

The most documented predictor of risk in relation to the occurrence of strokes in heart surgery is age [3]. However, there is a great variability in the studied populations and some assessed variables are not uniform, which make the validation of these data difficult. The prevalence of strokes increases dramatically with age. The risk of strokes in under 65-year-old patients is 0.9% and it is 8.9% in over 75-year-old patients [10]. A higher risk of strokes in the perioperative period has also been reported in patients with heart frequency disorders, the presence of thrombi in the left ventricle and significant atheroma in the aortic tomography [2]. Other risk factors found in the literature include preexisting cerebrovascular disease, peripheral vascular disease, hypertension and being a woman [1,6-9,11-14].

The current study was designed with the objective of evaluating the incidence and the predicting factors of postoperative major neurological dysfunction (defined as strokes) and the early clinical evolution in a non-selected cohort of patients submitted to CABG.

METHOD

Patient selection

A total of 1760 consecutive patients submitted to CABG without associated procedures but using CPB in the São Lucas Hospital of PUCRS in the period from January 1997 to February 2004 were included in this study.

Analyzed variables

The demographic and laboratorial variables, information on procedures and perioperative data were prospectively collected using the standardized protocol of the data registry of the Heart Surgery Recovery Unit (UPOCC) of São Lucas Hospital of PUCRS.

Variables considered to be potential risk predictors for cerebral ischemic events were subdivided according to the operative period into pre-operative (e.g. age, gender, presence of atrial fibrillation, ejection fraction), intra-operative (e.g. aortic clamping time, CPB time) and post-operative (e.g. shock, prolonged mechanical ventilation, atrial fibrillation).

Definitions

Major neurologic dysfunction was considered to be a focal lesion characterized by stroke (type I lesion). This was defined for any new neurologic deficit persisting for more than 24 hours confirmed by a neurologist in a physical examination and by brain imaging examinations (computed tomography or magnetic nuclear resonance), or stupor or coma at the time of hospital release.

The presence of prior cerebrovascular disease was specified by a history of strokes, transitory ischemic attacks (TIA) or surgical repair (carotid endarterectomy) in the patient's hospital records or by stenosis of the carotid artery = 50% seen by angiography, echography or magnetic angioresonance. Chronic renal insufficiency was defined as creatinine levels = 2 mg/dL in the pre-operative period. Left ventricular dysfunction was defined by a left ventricle ejection fraction (LVEF) = 40% identified by radioisotopic ventriculography and prolonged mechanical ventilation (PMV) was considered when it was required for more than 12 hours in the postoperative period.

Statistical analysis

Statistical analysis was performed using the SPSS program version 11.0 for Windows (Statistical Package for the Social Sciences, Inc). Initially, the characteristics of patients with and without stokes were compared. The data were expressed as percentages or as means ± standard deviation. For continuous variables, the Student t-test was utilized when the data presented with a normal distribution and the Mann-Whitney test for variables with non-Gaussian distributions. Categorical variables were compared using the Chi-squared or Fisher Exact tests.

Multivariable analysis was utilized to determine independent predictors of strokes in the post-operative period using the logistic regression method (Forward Wald), where variables with a p-value < 0.02 were included in the equation. For these results, ODDs ratios and 95% confidence intervals (95% CI) were calculated, with a p-value < 0.05 being considered statistically significant.

The present study was approved by the Scientific Research Committee of the Medical School of PUCRS and by the Research Ethics Committee of PUCRS.

RESULTS

Of the 1760 patients submitted to CABG without associated procedures, 52 (3%) evolved with major neurologic dysfunction (strokes) in the postoperative period. The pre-operative clinical characteristics of the patients are presented in Table 1.

The patients that evolved with major neurologic dysfunction were older (mean age 67 years old) and had a greater prevalence of chronic obstructive pulmonary disease (COPD) and prior cerebrovascular disease (CVD). Additionally, the mean serum fibrinogen was significantly higher in the group that evolved with strokes compared to the Control Group (461 vs. 245, respectively; p-value < 0.01).

In the trans-operative period, development of shock or severe hypotension was associated with the occurrence of major neurologic dysfunction (Table 2).

In relation to the postoperative variables, the presence of supraventricular tachycardia (atrial fibrillation or flutter), the occurrence of systemic inflammatory response syndrome (SIRS), shock and prolonged mechanical ventilation support were associated with the development of cerebral ischemic events (Table 2). Moreover, in the current study, the presence of stokes significantly increased the time of hospitalization and the in-hospital deaths (Table 2).

In the multivariate analysis, history of prior CVD and COPD proved to be independent predictors for the occurrence of major neurological dysfunction in the postoperative period of CABG without associated procedures. PMV also had an independent association with the outcome (Table 3). Prolonged hospitalization and mortality continued with statistical significance even after correction for possible confounding factors through multivariate analysis (Table 3).

Table 1. Pre-operative clinical characteristics

	Stroke (N=52)	without Stroke (N=1708)	p-value
Age: mean age ± SD	67±9.7	60±10	<0.001*
men	28	1129	NS
women	24	555	NS
risk factors: N (%)			
• Diabetes mellitus	20 (38)	476 (28)	NS
• Hypertension	39 (75)	1169 (68)	NS
• Alcoholics	3 (6)	48 (3)	NS
• Smokers	23 (44)	729 (43)	NS
• atrial fibrillation	3 (6)	48 (3)	NS
• COPD	17 (33)	320 (19)	0.02*
• Prior AMI	21 (40)	738 (43)	NS
• CVD	12 (23)	87 (5)	<0.001*
• Fibrinogen (N = 1302)	461±153	394±135	<0.01*
• aorta calcification (Rx)	6 (12)	116 (7)	NS
• CRF (Cr = 2)	2 (3,8)	79 (5)	NS
• Emergency CABG	1 (2)	1 (0,1)	NS
• peripheral arterial disease	5 (10)	138 (8)	NS
• LCT lesion	14 (27)	361 (21)	NS
• instable angina	24 (46)	707 (41)	NS
• Ejection fraction < 40% (N=1253)	8 (15)	345 (20)	NS

*N - absolute number; SD - standard deviation; NS - non-significant; COPD - Chronic obstructive pulmonary disease; AMI - acute myocardial infarction; CVD - cerebrovascular disease; CRF - Chronic renal failure; LCT - left coronary trunk; *variables considered statistically significant*

Table 2. Intra and post-operative variables

N (%)	Stroke (N= 52)	without Stroke (N= 1708)	p-value
intra-operative hypotension/Shock	2 (4)	9 (0.5)	0.04*
Time of CPB (N=1711)	95±26	82±53	NS
Time of clamping (N=1666)	52±19	48±22	NS
Fibrillation/atrial flutter	24 (46)	349 (20)	<0.001*
PMV	22 (42)	150 (9)	<0.001*
Shock	14 (27)	165 (10)	<0.001*
hypotension	11 (21)	347 (20)	NS
SIRS	8 (15)	105 (6)	0.02*
Time of hospitalization	18 ±14	10 ±7	<0.001*
Death	14 (27)	127 (7.3)	<0.001*

*N - absolute number; NS - non-significant; CPB - cardiopulmonary bypass; PMV - prolonged mechanical ventilation; SIRS - systemic inflammatory response syndrome; *: variables considered statistically significant*

Table 3. Independent association of variables with major neurological dysfunction in the postoperative period of coronary artery bypass surgery in isolation – multivariate analysis

	OR (95%CI)	p-value
PMV	7.5 (3.4-16.3)	<0.001*
CVD	5.9 (2.3-15.1)	<0.001*
COPD	2.8 (1.3-6.2)	0.012*

*OR - Odds ratio; CI - confidence interval; PMV - prolonged mechanical ventilation; COPD - Chronic obstructive pulmonary disease; CVD - cerebrovascular disease; *: variables considered statistically significant*

DISCUSSION

Neurologic complications after heart surgery procedures are a relatively common problem despite of the recent advances in the surgical and anesthetic techniques and the monitoring and perioperative management. Several previous studies have demonstrated non-negligible incidences for strokes in the postoperative period of CABG which varies from 0.4% to 14% depending on the population studied and the procedures performed [15]. In our sample, the incidence was 3%, a level similar to the two largest published series that evaluated more than 16,000 patients submitted to CABG and that reported rates of perioperative stroke of 2.0% and 4.6% [16,17].

The occurrence of strokes has important clinical and socioeconomic impacts. The hospitalization time is at least two times greater and the mortality rate can be sixteen times greater [18]. In our sample, the risk for death was 4.6 times higher in the group of patients who suffered strokes in the postoperative period and the time of hospitalization was almost doubled.

The importance of identifying the individual risk factors for neurological dysfunction is not only for an adequate stratification of surgical risk, but for the development of new strategies aiming at reducing the frequency of this complication.

Previous studies have proved that advanced age is an independent risk factor for the occurrence of perioperative strokes; however we believe that this variable is only a marker of advanced atherosclerotic disease and not the cause of strokes in itself. In our sample, age was associated with a greater risk of strokes in the univariant analysis, but it was not confirmed as an independent predictor of perioperative stroke, possibly because of the inclusion of other markers of atherosclerotic disease in our analytical model (peripheral vasculopathy, prior history of CVD, prior history of AMI, diabetes mellitus, hypertension and fibrinogen).

Some authors found that the aortic clamping time was a predictor of neurologic dysfunction [18,19]. In our study, the clamping time did not prove to be an independent predictor for strokes. A possible explanation would be that the importance of aortic clamping is related to the presence of plaques in the aorta and their location and not the time of clamping.

The association between atrial fibrillation and strokes, which has been described in many clinical situations including in the postoperative period of CABG, in our study was positive in the univariant analysis but with multivariate analysis, this association was not confirmed as an independent factor. A possible explanation is that in our service we immediately treat supraventricular tachycardia, attempting conversion to a sinus rhythm using antiarrhythmic drugs such as amiodarone, or by elective cardioversion when there is hemodynamic stability. Additionally, if the atrial fibrillation continues for more than 48 hours, the patient is treated with anticoagulation.

In our study we found as the main predicting factor for the occurrence of perioperative strokes a prior history of CVD with an ODDs ratio of 5.9 and an incidence of strokes of 23% in this subgroup. This denotes the existence of changes in the cerebral circulation system and consequently an increased risk for cerebrovascular events. Prior publications demonstrate an incidence of perioperative strokes in patients with CVD of from 7% to 16.8%, however, on the contrary to our study, they did not include in the definition of prior CVD the presence of carotid stenosis > 50% or a history of carotid endarterectomy, but only the prior occurrence of strokes or TIA. Another condition that might cause the higher number of strokes in this group in our study is the fact that a trans-operative echocardiogram is not routinely indicated to assist in the identification of the aortic clamping site. Additionally, the carotid arteries are not routinely assessed by echocardiography in over 65-year-old patients or those with lesions of the left coronary artery trunk, which are associated with carotid disease [15,17,20].

Another variable which continued to be independently associated was COPD. Patients with COPD presented with an accentuated pre-thrombotic condition due to the increase in the viscosity of the blood and endothelium dysfunction associated to systemic inflammation [21]. Moreover, these patients frequently suffer comorbidities such as atherosclerosis and systemic vascular disease and are often smokers [17].

PMV was the only postoperative factor that demonstrated an independent association with the outcome under study. The occurrence of strokes in the postoperative period of CABG reduces, to differing degrees, the level of consciousness of patients, making early weaning from mechanical respiratory support difficult. Additionally, as has

previously been reported, strokes also induce higher incidences of respiratory infection and, for this and other reasons, there is a greater risk of respiratory insufficiency and the necessity to reconnect the mechanical respiratory support [14,22]. It has already been proven that this sequence of events is associated with a longer hospitalization and longer periods in the intensive care.

Not performing neuropsychological tests capable of detecting slight changes in mental, cognitive or behavioral states was a limitation of our study; however, these tests are efficacious in the evaluation of less important neurologic events (type-II neurological dysfunction) which was not our objective in this investigation. More detailed information related to the cerebrovascular event such as the moment, severity, type and location of the stroke, which could be included in the analysis to identify a subgroup within the sample, might also constitute a limitation of the study.

However, some points deserve mentioning such as the presence of a significant sample size from a single institution which has standardized pre-, trans- and post-operative techniques which prevent bias in the study. The inclusion of patients submitted to CABG without associated procedures is a factor which we consider to be of fundamental importance and which was not used in the majority of published investigations. It is well known that any other procedure that is performed during CABG increases the surgical times (aortic clamping and cardiopulmonary bypass) and that these have proved, in some articles, to be important predictors of adverse clinical events including strokes, which was confirmed in our study. Moreover, it is known that open heart surgery, involving either the ventricle or the atrium, increases the risk of embolic events including strokes compared to surgeries where the cavities are not opened. Finally, the sample composed only of patients undergoing CABG as an isolated procedure, excludes valve replacement surgeries required due to infectious endocarditis, which, in itself, increases the risk of strokes; these cases were included in some previously published series [17].

In conclusion, strokes are a feared postoperative complication that until today affects a significant number of patients submitted to CABG. With our study, we proved that the presence of prior CVD is a pre-operative risk factor; we suggest planned individual strategies of patient management for this subgroup of patients. Additionally, the presence of COPD, to a lesser degree, was also found to be a predictor of new cerebrovascular events, supporting previously available information that these patients have a higher surgical risk.

In parallel, the occurrence of PMV in the postoperative period of this study proved to be a factor significantly associated with strokes. This is important to increase the precautions taken in respect to new cerebrovascular events in patients after CABG with difficult or slow weaning from mechanical respiration support.

Finally, we saw the importance of the occurrence of major neurological dysfunction, not only in terms of morbidity and limited function for the patient, but also in the increased hospital costs due to the longer hospitalization time and the solid result with an increase in mortality. This is a similar conclusion to previous publications that also reported high mortality rates (13%-41%) in patients who suffer strokes after CABG [1].

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