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Stroke After Coronary Bypass Surgery Is Mainly Related to Diffuse Atherosclerotic Disease

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ABSTRACT

Objective: This study aims to investigate the risk factors for postoperative stroke and analysis of outcome after coronary bypass surgery with cardiopulmonary bypass.

Methods: Between 1999 and 2008, 3248 consecutive patients who underwent isolated coronary surgery with cardiopulmonary bypass were prospectively enrolled in the study. Demographic and perioperative data were analyzed. Postoperative stroke was defined as severe adverse neurological events including permanent deficits or cerebral lesions with radiological demonstration of cerebral infarction within the first postoperative month.

Results: In total, 32 patients (0.9%) were determined with stroke. Univariate risk factors for postoperative stroke were determined as preoperative unstable angina (P = .006), Canadian Class of Angina (CCA) ≥ 3 (P = .001), preoperative creatinin level >1.2 mg/dL (P = .001), left main coronary artery disease (P = .04), chronic obstructive lung disease (P = .04), peripheral arterial disease (P < .001), New York Heart Association (NYHA) Class ≥ 3 (P = .004), preoperative renal insufficiency (P = .001), age > 65 years (P = .04), preoperative hypothyroidism (P = .02), postoperative low cardiac output state (P < .001), severe coronary artery disease requiring distal anastomosis ≥ 4 (P = .05), non-elective operation (P = .02), and body mass index ≥ 25 (P = .02). Multivariate analysis revealed peripheral arterial disease (odds ratio [OR], 5.2; 95% confidence interval [CI], 1.9-14.0; P = .001), severe coronary artery disease (OR, 3.1; 95% CI, 1.1-8.5; P = .02), and postoperative low cardiac output state (OR, 5.1; 95% CI, 1.4-18.2; P = .01) as the independent risk factors.

Conclusions: Stroke after coronary bypass surgery with cardiopulmonary bypass is mainly related to diffuse atherosclerotic disease.

INTRODUCTION

Despite the increasing age, morbidity, and severity of coronary artery disease, outcome after coronary bypass surgery has improved in general; however, postoperative neurological adverse events remained as an exception [Charlesworth 2003; McKhann 2006; Anyanwu 2007]. Postoperative stroke is currently described as the major drawback of coronary bypass surgery to compete with any other kind of treatment modality such as percutaneous coronary interventions [Morice 2010]. Current studies report stroke rates after coronary bypass surgery between 0.8% and 6%, and mortality after postoperative stroke is reported to be between 14% and 36% [Patel 2002; Charlesworth 2003; McKhann 2006; Anyanwu 2007; Chu 2009; Morice 2010]. Although there has been development of new surgical techniques and superior perioperative care, the rate for postoperative stroke did not differ significantly and the mortality associated with perioperative stroke has been constant over the past 3 decades [Charlesworth 2003; McKhann 2006; Anyanwu 2007].

Efforts to overcome this devastating complication informed us that off-pump technique may be a modification to overcome this specific problem, but there is still a controversy on that issue [Patel 2002; Chu 2009]. The majority of coronary bypass operations are still performed with cardiopulmonary bypass (CPB) due to surgeon choice or technical reasons. Thus neurological adverse event still comes up to be the major postoperative complication and should be further investigated.

This study aims to investigate the risk factors for postoperative stroke and analysis of outcome after coronary bypass surgery with cardiopulmonary bypass.

MATERIAL AND METHODS

This study included evaluation of prospectively collected data from consecutive isolated coronary artery bypass surgery procedures performed by one surgical and anesthesia team between 1999 and 2008. A total of 3248 patients were evaluated.

The main end point of the study was occurrence of postoperative stroke and related outcome. Postoperative stroke was defined as severe adverse neurological events including permanent deficits or cerebral lesions with radiological demonstration of cerebral infarction within the first postoperative month. All patients with stroke were evaluated by a neurologist. These patients' cases were also documented with a recommended imaging test (magnetic resonance imaging [MRI] or computed tomography [CT]).

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Table 1. Preoperative and Intraoperative Variables*

	Postoperative Stroke – (n = 3216; 99.1%)	Postoperative Stroke + (n = 32; 0.9%)	*P*
Mean age, y	60.6 ± 9.5	63.2 ± 7.4	NS
Euroscore, %	3.6 ± 2.5	4.4 ± 3.7	NS
Euroscore > 5, %	21.6	31.3	NS
Female sex, %	22.5	28.1	NS
Preoperative congestive heart failure, %	1.8	6.3	NS
Preoperative hematocrit < 30%, %	2.6	4.2	NS
Smoking (current and previous), %	67.1	62.5	NS
Hypertension, %	48.7	62.5	NS
Diabetes mellitus, %	24	31.3	NS
Hyperlipidemia, %	44.5	43.8	NS
Preoperative use of aspirin, %	57.8	59.4	NS
Preoperative use of clopidogrel, %	4	6.3	NS
Preoperative use of beta blockers, %	43.2	43.8	NS
Preoperative use of calcium antagonists, %	20.5	28.1	NS
Preoperative use of ACEI, %	27.5	31.3	NS
Preoperative use of diuretics, %	6.1	9.4	NS
Preoperative use of oral nitrate, %	48	62.5	NS
Preoperative use of intravenous nitrate, %	5.8	12.5	NS
Preoperative use of intravenous inotrope, %	0.5	3.1	NS
Redo operation, %	1.9	3.1	NS
Perioperative use of tranexamic acid, %	12.7	15.6	NS
Perioperative use of aprotinin, %	5.6	7.1	NS
Preoperative atrial fibrillation or flutter, %	0.8	1.4	NS
Preoperative use of levosimendan, %	0.2	0	NS
Cross-clamp time, min	33 ± 13	32 ± 12	NS
Cardiopulmonary bypass time, min	58 ± 21	59 ± 22	NS
Cross-clamp time > 40 min, %	23.5	29	NS
Cardiopulmonary bypass time > 60 min, %	43.2	51.6	NS
Postoperative drainage, mL	599 ± 337	693 ± 467	NS
Postoperative dranage > 1000 mL, %	9.6	19.4	NS
Perioperative blood transfusion, %	30.2	40.6	NS

*ACEI indicates angiotensin converting enzyme inhibitors.

The primary aim of the study was to investigate postoperative stroke in patients treated with cardiopulmonary bypass. Patients treated with off-pump technique were excluded. The total number of excluded patients was 348 (9%) among 3596 total coronary bypass cases within the defined period. We basically have chosen the operative technique according to the coronary lesion set: off-pump technique was performed in patients with isolated left anterior descending artery disease with or without diagonal branch lesions, who had a vessel diameter of > 2mm, no diffuse atherosclerotic disease and no intramyocardial course. The mean number of bypassed vessels in this group was lower than in the group of patients treated with cardiopulmonary bypass. Thus exclusion of this group led us to establish a more uniform group of patients.

Preoperative assessment of the ascending aorta for extensive calcification, with non-invasive imaging techniques such as computed tomograhy, was only performed in patients with a documented preoperative extensive calcification images on chest x-ray. No epiaortic ultrasound imaging was used. In 14 patients with multivessel coronary artery disease and severe ascending aortic calcified atheromas, the ascending aorta was replaced with tubular graft interposition under deep hypothermia and circulatory arrest. This group of patients with a combined procedure was excluded.

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Table 2. Risk Factors for Postoperative Stroke (Univariate Analysis)

	Postoperative Stroke – (n = 3216; 99.1%)	Postoperative Stroke + (n = 32; 0.9%)	*P*
Preoperative unstable angina, %	0.9	5.9	.006
NYHA ≥ 3, %	8.9	25	.003
CCA ≥ 3, %	34	75	.001
Body mass index > 25, %	76.2	59.4	.02
Age > 65 y, %	36.9	53.1	.045
Chronic obstructive lung disease, %	15.2	28.1	.04
Preoperative hypothyroidea, %	2	9.4	.02
Number of distal anastomosis ≥ 4, %	8.8	18.8	.05
Preoperative creatinin level > 1.2, %	9	33.3	.001
Peripheral arterial disease, %	5.7	26.7	<.001
Left main coronary artery disease, %	4.8	12.5	.04
Postoperative low cardiac output, %	2.3	18.8	<.001
Nonelective operation, %	11.4	25	.02
Preoperative cerebral event†, %	5.4	25	.001

*NYHA indicates New York Heart Association class; CCA, Canadian Class of Angina.

†Preoperative cerebral event included stroke or transient ischemic attack.

Patients who underwent concomitant carotid and coronary surgery and patients with severe carotid stenosis (>70% stenosis) were also excluded.

Anesthesia and Operative Technique

Anesthetic induction consisted of midazolam 50 g/kg, pancronium 0.15 mg/kg, and fentanyl 25 to 35 g/kg. After endotracheal intubation, 50% O_2, 50% N_2O, and 3% to 4% desflurane was used for all hemodynamically stable patients. Tranexamic acid (20 mg/kg over 20 minutes) was administered before CPB in patients who received this medication. This protocol was performed consecutively in all patients who underwent operations since October 2006. During CPB, mean arterial pressure and pump flow were kept between 50 and 80 mmHg and 2.2 to 2.5 L/m^2, respectively. Adequacy of tissue perfusion was monitored with arteriovenous partial carbon dioxide difference (P_{v-a} CO_2), lactate level, urine output, and base deficit. Moderate hypothermia (32°C) was used during CPB. Myocardial viability was preserved with antegrade cold hyperkalemic crystalloid cardioplegia (Plegisol®, Abbott Laboratories, Abbott Park, IL, USA) except in patients with a left ventricular ejection fraction less than 0.25 in whom antegrade + retrograde blood cardioplegia associated with terminal warm blood cardioplegia was used. In patients with ejection fraction <30%, levosimendan infusion was used for 24 hours (0.2 g/kg per min) starting 4 hours preoperatively. After the termination of CPB, midazolam and vecuronium dose was decreased to 50 g/kg per hour and discontinued at skin closure.

Postoperative Clinical Management

Basic fluid substitution during the first 20 postoperative hours was 40 mL/kg per day; 600 to 800 mL of this solution was the autologous blood derived from CPB circuit, and the rest was balanced crystalloid solution. All patients were evaluated for extubation every half hour. As soon as spontaneous breathing resumed, respiratory rate was gradually decreased to 4/min and pressure support to 4 mmHg. All hemodynamically stable patients without excessive chest tube drainage and P_aCO_2 < 48 mmHg, pH > 7.30, and P_aO_2/FiO_2 > 250 were extubated. Aprotinin had been administered postoperatively in patients with massive bleeding according to the decision of the surgeon and the anesthesiologist in dosage of 1,000,000 IU in patients operated on before 2005.

We aimed to discharge all patients on the fifth postoperative day. The decision to discharge is based on a satisfactory routine checkup on day 4 consisting of clinical examination, full blood cell count, urea and electrolyte levels, electrocardiogram, and chest roentgenogram. If the patient is medically unfit on day 5, hospitalization is prolonged, and further investigations may be performed depending on the clinical status.

Data Source and Definitions

Our clinical database is used for outcome analysis. It is a prospectively collected record containing relevant patient demographic data, comorbidities, intraoperative variables, and postoperative outcome including postoperative drainage, ventilation time, intensive care unit (ICU) stay time, hospital stay time, transfusion rate, new onset postoperative renal failure, postoperative stroke, reoperation, arrhythmia, rate of readmission to the intensive care unit, rate of readmission to the hospital, and mortality.

Hospital mortality included all deaths within 30 days of operation irrespective of where the death occurred and all deaths in the hospital after 30 days among patients who had not been discharged after the operation. Postoperative blood

Table 3. Risk Factors for Postoperative Stroke (Multivariate Analysis)

	Odds Ratio	95% Confidence Interval	*P*
Peripheral arterial disease	5.2	1.9-14.0	.001
Postoperative low cardiac ouput	5.1	1.4-18.2	.01
Severe coronary artery disease	3.1	1.1-8.5	.02

Table 4. The Effect of Stroke on Outcome Parameters*

	Postoperative Stroke – (n = 3216; 99.1%)	Postoperative Stroke + (n = 32; 0.9%)	*P*
Ventilation time, h	4.8 ± 7.1	13.2 ± 19.7	<.001
Ventilation time > 8 h, %	7.4	32.1	<.001
ICU stay time, h	22.1 ± 19	46.9 ± 61	<.001
ICU stay time > 24 h, %	4.2	32.1	<.001
Hospital stay time, d	5.3 ± 3.4	11.3 ± 11.4	<.001
ICU readmission, %	1.7	25	<.001
Need for reentubation, %	1.2	20	<.001
Hospital readmission, %	3.1	NA	NA
New onset atrial fibrillation, %	9.9	21.4	<.001
Mortality, %	0.8	18.7	<.001

*ICU indicates intensive care unit; NA, not available (some of the patients with stroke were transferred to another unit or hospital, thus readmission to the hospital was not measurable).

loss was defined as total chest tube drainage.

Statistical Analysis

Data are reported as a percentage or as a mean standard deviation. Univariate comparisons were computed using the χ^2 test or Fisher's exact test for categorical variables and *t* tests for continuous variables. Any factor with a *P* value of less than .1 on univariate analysis was entered into multiple logistic regression. Statistical analysis was performed using SPSS statistical software (SPSS version 11.0, SPSS Inc, Chicago, IL, USA). Variables were considered significant at *P* values less than .05. Multivariate logistic regression analysis was performed to define independent risk factors for postoperative stroke.

RESULTS

Demographic and peroperative variables are shown in Table 1. In total, 32 patients (0.9%) were determined with stroke. Univariate risk factors for postoperative stroke were determined as preoperative unstable angina (*P* = .006), Canadian Class of Angina (CCA) ≥ 3 (*P* = .001), preoperative creatinin level > 1.2 (*P* = .001), left main coronary artery disease (*P* = .04), chronic obstructive lung disease (*P* = .04), peripheral arterial disease (*P* < .001), New York Heart Association (NYHA) Class ≥ 3 (*P* = .004), preoperative renal insufficiency (*P* = .001), age > 65 years (*P* = .04), preoperative hypothyroid (*P* = .02), postoperative low cardiac output state (*P* < .001), severe coronary artery disease (requiring distal anostomosis ≥ 4)

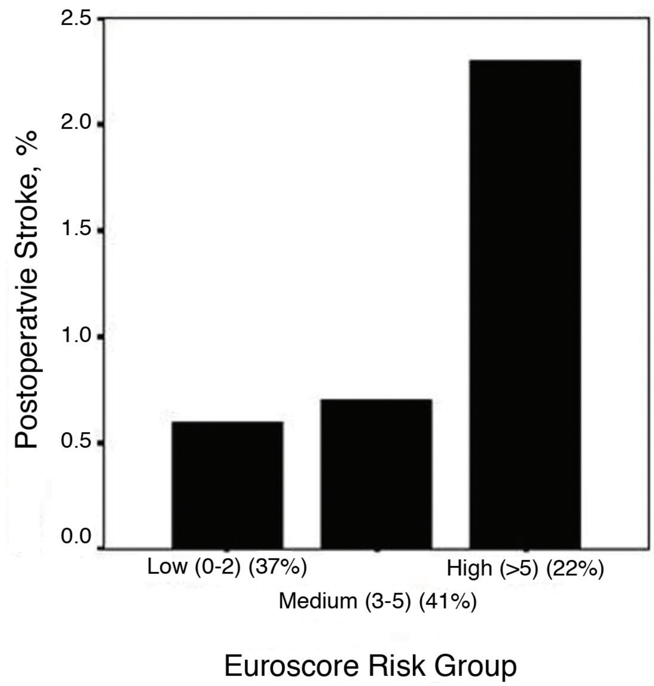

Figure 1. Postoperative stroke according to the Euroscore risk groups.

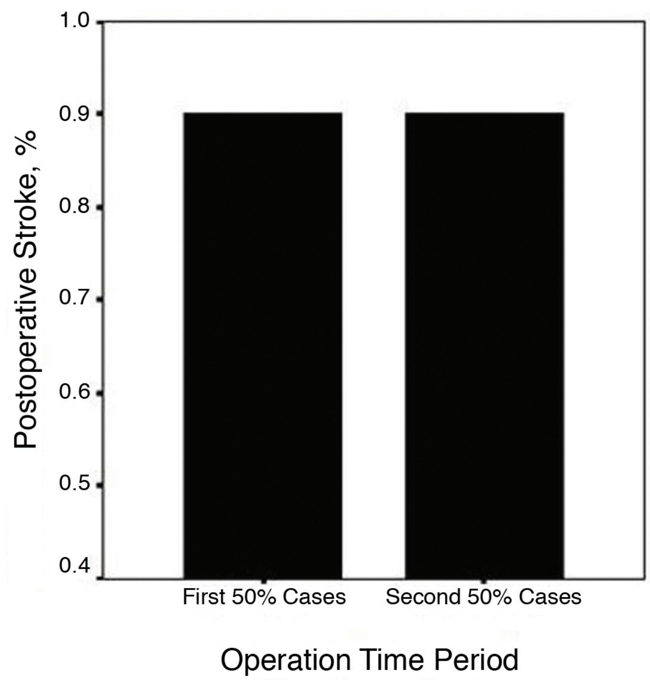

Figure 2. Postoperative stroke according to the operation time period.

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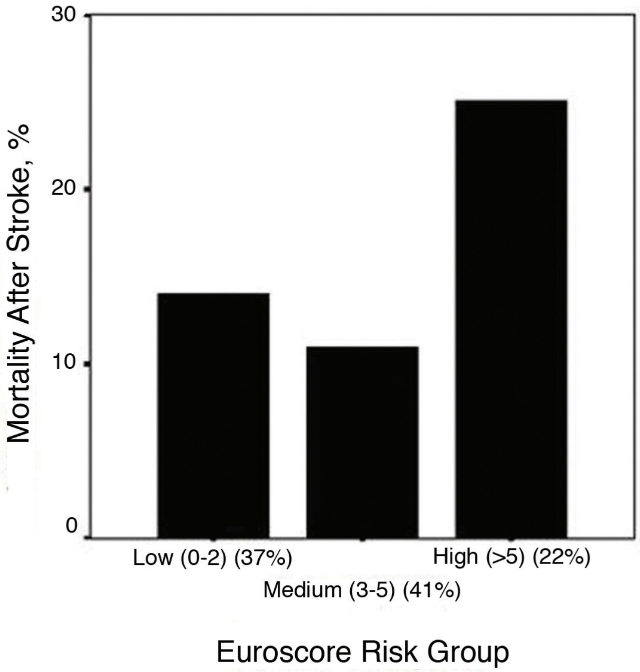

Figure 3. Postoperative mortality according to the Euroscore risk groups in patients with postoperative low cardiac output.

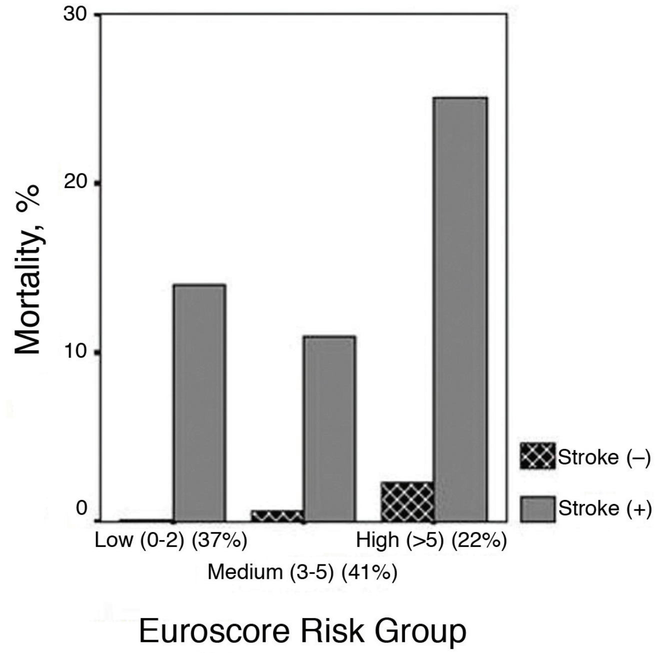

Figure 4. Postoperative mortality according to the Euroscore risk groups and occurrence of stroke.

(P = .05), non-elective operation (P = .02), and body mass index ≥ 25 (P = .02) (Table 2).

Multivariate analysis revealed peripheral arterial disease (odds ratio [OR], 5.2; 95% confidence interval [CI], 1.9-14.0; P = .001), severe coronary artery disease (OR, 3.1; 95% CI, 1.1-8.5; P = .02), and postoperative low cardiac output state (OR, 5.1; 95% CI, 1.4-18.2; P = .01) as the independent risk factors (Table 3). The effect of postoperative stroke on outcome is shown in Table 4.

The analysis according to the Euroscore risk groups (low-risk group, Euroscore = 0-2, n = 1200 [37%]; medium-risk group, Euroscore = 3-5, n = 1332 [41%]; high-risk group, Euroscore ≥ 6, n = 716 [22%]) revealed that postoperative stroke occurred at a higher rate in the high-risk group when compared to the moderate- and the low-risk group (2.3% versus 0.7% versus 0.6%, respectively) (P = .03) (Figure 1). The analysis according to the operation time period (the first half and the second half of the patients) revealed that postoperative stroke occurred at the same rates in both groups (0.9% versus 0.9%) (Figure 2).

Low cardiac output state was defined in 78 patients (7.6% of the total group; 18.8% in patients with stroke and 2.3% in patients without stroke, P < .001). The stroke rate after the development of low cardiac output was higher in the high-risk group than in the medium- or low-risk groups (10.2% versus 3.8% versus 7.6%, respectively; P = .04) (Figure 3).

Mortality in patients with stroke was higher when compared to patients without stroke (18.7% versus 0.8%; P < .001). Mortality after stroke was determined to occur at a higher rate in the high-risk group when compared to the moderate- and low-risk groups (25% versus 11% versus 14%, respectively; P = .03). Mortality rates in patients with no stroke were defined as 2.3% versus 0.6% versus and 0.1%, respectively (Figure 4).

Comment

The main finding of the study is the demonstration of the risk factors for postoperative stroke after isolated coronary bypass surgery with cardiopulmonary bypass in a homogeneous population of patients. The strongest preoperative determinant for postoperative stroke was peripheral arterial disease with an odds ratio equal to 5.3. The other independent risk factors were defined as severe coronary artery disease and postoperative low cardiac output state, which also represent the signs of diffuse atherosclerotic disease.

Secondly this study demonstrated a wide range of severe adverse outcome including prolonged intubation time, prolonged ICU stay time, prolonged hospital stay time, increased ICU readmission rate, increased need for re-intubation, increased rate of new onset atrial fibrillation, and increased mortality related with postoperative stroke.

Regarding to these findings the related topics below should be discussed:

1. Epidemiology of Stroke. The incidence of postoperative stroke was 0.9% in this uniform group of patients. This incidence of a low stroke rate when compared to other series may be associated with stroke prevention applications like hypothermia or maintenance of high perfusion pressure. What is more important is that this rate did not change in time, and it was the same in patients operated on between

1999 and 2003 (the first 50% of cases) and between 2004 and 2008 (the second 50% of the patients). In literature, series between the early 1980s and the 2000s report rates of postoperative stroke also to remain constant for a specific study population in consecutive time periods that vary within the range of 0.8%-6% [Charlesworth 2003; McKhann 2006; Anyanwu 2007]. Although there have been alterations in different factors effecting the occurrence of postoperative stroke (increased morbidity, advances in perioperative management), detection of no major change in postoperative stroke rate implies that an unmodifiable or simply an underestimated risk factor may exist.

Data in the literature reports a wide range of independent risk factors related to surgical complexity, atherosclerotic disease, or the critical preoperative status of the patient for postoperative stroke after cardiac surgery in general. These factors include aortic surgery, redo operation, chronic renal failure, blood transfusion, previous stroke, critical preoperative status, age > 60 years, poor left ventricular function, female sex, diabetes mellitus, peripheral vascular disease, unstable angina, and pulmonary hypertension [Breuer 1983; D'Ancona 2000; Puskas 2000; Stamou 2001; Patel 2002; Chu 2009]. However, a relatively limited number of risk factors have been defined for isolated coronary bypass operations that mainly focus on the myocardial dysfunction and vascular disease. Because the preoperative and operative variables are restricted to a more specific field and purified from widely known stroke inducing factors such as manipulating the aorta and aortic branches during aortic surgery or clamping the carotid arteries in a combined procedure, documentation of a causative relation between operation-specific techniques and stroke could be more facilitated in isolated coronary bypass surgery. Thus any unmodifiable or underestimated risk factor can be defined more precisely. In the context of our results, peripheral arterial diseases or severe coronary artery diseases, which are indicators of diffuse atherosclerotic disease, can be recognized as such unmodifiable factors. Postoperative low cardiac output state, which was detected as an independent risk factor, can also be partially associated with the severity of diffuse atherosclerotic disease. In the absence of complicative perioperative myocardial protection, which is currently so unusual for isolated coronary bypass operations, low cardiac output may basically be induced by previous myocardial infarction or emergency due to acute myocardial ischemia or failed angioplasty, which together lead us to focus on the severity coronary artery disease again. Moreover, analysis of postoperative stroke rates in patients with low cardiac output reveals that stroke mainly occurs in the high Euroscore risk group, which means that high cardiovascular risk contributes to occurrence of stroke in the presence of an independent risk factor. This may imply that low cardiac output state has both causation and association link with postoperative stroke.

2. Issue of Peripheral Arterial Disease. Peripheral arterial disease was defined as the strongest predictive factor of stroke in our study. This factor has been involved in the risk assessment of cardiac surgery; however, it is omitted from all guidelines for treatment prevention and rehabilitation of stroke [Banerjee 2010]. Actually it is defined as a stronger predictor of concurrent stroke risk than coronary artery disease. Presence of peripheral arterial disease is reported in 5.9% of patients with transient ischemic attack, 8.9% of patients with minor stroke, and 14.4% of patients with major stroke in the normal population [Banerjee 2010]. The sensitivity and specificity of diagnosis of peripheral arterial disease to predict stroke is reported to be 93% and 41% respectively [Doobay 2005]. Taking into account the reported association between peripheral arterial disease and stroke in the normal population and the incidence of peripheral arterial disease in coronary surgery patients, it may be assumed that it is acceptable to face postoperative stroke in the previously reported range of rates after coronary bypass surgery. This may give rise to the conception that coronary bypass surgery may be just the trigger not the primary causative factor for stroke.

3. Effect of Stroke on Outcome. Patients diagnosed with postoperative stroke had a 23-fold increased risk of 30-day mortality when compared to patients with no stroke in our study (18.7% versus 0.8%). This statement of poor survivorship after stroke may imply that preventive policies for postoperative stroke should have more importance attached to them. Although the maximum levels of mortality after stroke was defined in the high Euroscore risk group, the relative amplifier effect of stroke on mortality was more prominent in the low Euroscore risk group (14% versus 0.1%). Unlike the relation between low cardiac output and the occurrence of stroke, this implies that postoperative stroke increases the risk of mortality irrespective to the morbidity or the preoperative complexity of the patient.

The literature data confirm our disproportionally increased rate of mortality in patients with stroke. The reported mortality rates vary between 14% and 36%. Moreover, the effect of stroke on mortality continues even after the hospital discharge. The long-term survival rates in patients with postoperative stroke are reported to be between 63% and 83%, 44% and 58%, and 27% and 36% in 1, 5, and 10 years, respectively, which are quite lower than reported survival rates after uncomplicated isolated coronary bypass surgery (94% for 1 year, 83% to 94% for 5 years, and 60% to 61% for 10 years) [Puskas 2000; Ascione 2002; Dacey 2005; Bronster 2006].

Our study also defined prolonged ICU stay time in patients with postoperative stroke. These patients required longer periods of intubation time and a higher rate of reintubation, which means additional need for intense medical therapy and medical resources.

These patients also required prolonged hospital stay, increased rate of ICU readmission, increased rate of hospital readmission, and increased rate of new onset atrial fibrillation, which further increased the mortality, morbidity, and use of medical resources.

4. Prevention of Stroke. Several protective efforts against postoperative stroke have been introduced. These include usage of epiaortic ultrasound, single clamp technique, maintenance of high perfusion pressures, and hypothermia [Aranki 1995; Gold 1995; Zingone 2006]. However, the major focused factor is still the implementation of off-pump technique. Avoidance of cardiopulmonary bypass and aortic crossclamping may decrease the risk of embolization from aortic

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atheromas. It has been reported in some studies that there is an independent effect of avoiding cardiopulmonary bypass on neurologic outcome and that off-pump technique is the sole protective factor against stroke, providing a lower stroke and stroke-related mortality rate after coronary bypass surgery [Bucerius 2003; Brizzio 2010]. However reports underlining the opposite also exist [Chu 2009].

In our study population, a relatively small number of patients with 1 or 2 vessel disease were operated with off-pump technique; the stroke rate was 0.7% in this group. These patients were excluded from the study to eliminate the possible bias effect.

Moreover, the object of the study was not to investigate the effect of off-pump surgery but to define the strongest risk factors for stroke in a more uniform group.

CONCLUSIONS

This study investigated postoperative stroke in a uniform group of patients operated for isolated coronary bypass surgery with cardiopulmonary bypass. Excluding the widely known factors associated with the occurrence of stroke, such as carotid stenosis, combined procedures, or off-pump technique, our findings suggest that unmodifiable risk factors such as diffuse atherosclerotic disease exist for development of stroke. Although a low incidence of postoperative stroke was demonstrated in a uniform group of patients, the occurrence of stroke was related with disproportionally increased risk of mortality and morbidity even in the low risk group. Taking into consideration the devastating adverse outcomes of postoperative stroke and the existence of unmodifiable risk factors, we may assume that detection of a high-risk patient group with coronary artery disease for postoperative stroke may help us only a little to modify the operative technique, at least in the present setting of coronary bypass surgery with cardiopulmonary bypass; however, it can improve the quality of our decision making for accepting or rejecting a patient for surgery or referring him or her for another treatment modality such as off-pump or hybrid revascularization techniques.

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