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Chronologic Distribution of Stroke After Minimally Invasive Versus Conventional Coronary Artery Bypass

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OBJECTIVES We sought to investigate whether the chronologic distribution of the onset of stroke occurring after coronary artery bypass graft surgery (CABG) without cardiopulmonary bypass (off-pump CABG) is different from the conventional on-pump approach (CABG with cardiopulmonary bypass).

BACKGROUND Off-pump CABG has been associated with a lower stroke rate, compared with conventional on-pump CABG. However, it is unknown whether the chronologic distribution of the onset of stroke is different between the two approaches.

METHODS We evaluated the chronologic distribution of postoperative stroke in patients undergoing CABG from June 1996 to August 2001 (n = 10,573). Preoperative risk factors for stroke were identified using the Northern New England preoperative estimate of stroke risk. Multivariate logistic regression analysis was used to determine the independent predictors of early stroke and to delineate the association between the surgical approach and the chronologic distribution of the onset of stroke.

RESULTS Stroke occurred in 217 patients (2%, n = 10,573). A total of 44 (20%) and 173 (80%) of these patients had stroke after off-pump CABG and on-pump CABG, respectively. The median time for the onset of stroke was two days (range 0 to 11 days) after on-pump CABG versus four days (range 0 to 14 days) after off-pump CABG ($p < 0.01$). On-pump CABG was associated with a higher risk of early stroke (odds ratio 5.3, 95% confidence interval 2.6 to 10.9; $p < 0.01$) compared with off-pump CABG.

CONCLUSIONS Compared with off-pump CABG, on-pump CABG is associated with an earlier onset of postoperative stroke during the recovery phase, suggesting different mechanisms in the pathogenesis of stroke between the two surgical approaches. (J Am Coll Cardiol 2004;43: 752–6) © 2004 by the American College of Cardiology Foundation

Coronary artery bypass graft surgery (CABG) is associated with a high risk of various neuropsychological complications, stroke being the most serious (1). Different risk factors predisposing to postoperative stroke after conventional cardiopulmonary bypass (CABG with cardiopulmonary bypass [on-pump CABG]) include advanced age, carotid artery disease, hypertension, depressed ejection fraction, manipulation of the aorta, and postoperative atrial fibrillation (2–10). Preliminary studies reported a reduced postoperative stroke rate after CABG without cardiopulmonary bypass (off-pump CABG) (5). However, previous studies have considered stroke as a single end point without consideration of when the event occurred in the recovery phase.

The current study was conducted in a large clinical setting to systematically investigate whether off-pump CABG is associated with a different chronologic distribution of the onset of stroke than conventional on-pump CABG.

METHODS

Patients. The patients gave written, informed consent for all procedures performed. The study was approved by the Medstar Research Institute's Review Board. The computerized data base of the Section of Cardiac Surgery of the Washington Hospital Center was used to identify all patients who underwent CABG (n = 10,573) between June 1996 and August 2001. During that period, 3,268 patients had off-pump CABG performed, whereas 7,305 patients had on-pump CABG. A total of 217 patients were diagnosed with postoperative stroke, 44 (20%) of whom had off-pump CABG and 173 (80%) of whom had on-pump CABG. The chronologic distribution of stroke, in days from the surgery date and other clinical events, were source-documented and adjudicated. Strokes were confirmed by an independent neurologist and/or by appropriate brain imaging. Baseline demographics, procedural data, and perioperative outcomes were recorded and entered prospectively in a prespecified database by a dedicated data coordinating center.

Operative techniques. Routine anesthesia and intraoperative monitoring protocols were applied in both groups. On-pump CABG was performed using standard median sternotomy, extracorporeal circulation, and myocardial protection methods. Partial cross-clamping of the aorta was used to perform proximal anastomoses. Myocardial protection was obtained using anterograde and retrograde cardioplegia, as chosen by the surgeon. The patients were cooled to 34°C. The air was evacuated from the heart/aorta

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
off-pump CABG	= CABG without cardiopulmonary bypass
on-pump CABG	= CABG with cardiopulmonary bypass
NNE	= Northern New England

through an aortic needle vent. The perfusion pressures were maintained at 60 mm Hg. Off-pump CABG was performed using either a median sternotomy or an anterior or lateral minimally invasive direct coronary artery bypass approach. Intracoronary shunts were not routinely used during the procedure. Indications for these approaches (5) and selection criteria for off-pump CABG (12) have been described elsewhere.

Definitions. OPERATIVE VARIABLES. Atherosclerosis of the ascending aorta was defined as circumferential involvement of most or all of the ascending aorta, ulcerated plaques, large and mobile or protruding atheromata, thrombi, or operator-identified diffuse irregularities (13).

POSTOPERATIVE VARIABLES. Prolonged ventilation was defined as the need for respiratory support for more than 24 h. Perioperative myocardial infarction was diagnosed if at least two of the following four criteria were met: 1) prolonged typical angina (>20 min), 2) positive cardiac enzymes, 3) changes on serial echocardiography consistent with infarction, and 4) at least two serial electrocardiographic tracings showing new ischemic changes. Low cardiac output syndrome was defined as the use of postoperative inotropic support for >24 h. Postoperative stroke was defined as any new permanent global or focal neurologic deficit presenting in the hospital and persisting for more than 72 h (2).

Statistical analysis. Preoperative risk factors for stroke were defined using the definitions from the Northern New England (NNE) preoperative estimate of stroke risk (14). Comparisons of ordinal categorical data were done using the Cochran-Armitage test for trends. All other comparisons were made using the chi-square test for general association (or the Fisher exact test when the assumptions of the chi-square test were not met). The NNE stroke risk score was computed, adjusted, and compared between the surgery types, using the Wilcoxon sign-rank test. All tests are two-sided. A logistic regression model was used to test the association between surgery type and preoperative risk factors and between surgery type and chronologic distribution of stroke. Multicollinearity among the independent variables was assessed using Pearson's correlation and tolerance. The maximum likelihood approach was used to compute the estimates. Three goodness-of-fit measures were used to evaluate model fit: deviance, Pearson's, and Hosmer and Lemeshow. Only the Hosmer and Lemeshow goodness-of-fit statistic is reported. The relationship between preoperative risk factors and the chronologic distribution of the onset of stroke (in quartiles) was tested using a cumulative logit model adjusting for preoperative risk factors. The proportional odds assumption was tested. The score test for the proportional odds assumption was used. A p value of 0.10 was obtained. Fit was further tested by the overall goodness-of-fit tests. A value of $p < 0.05$ was considered statistically significant.

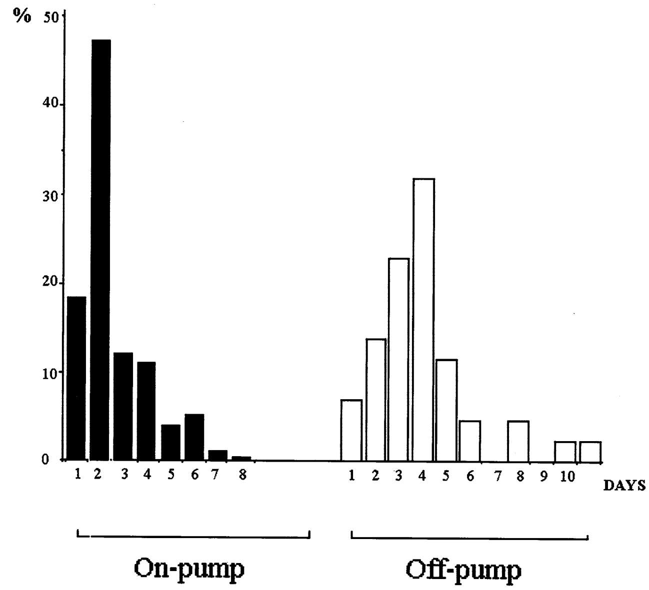

Figure 1. Chronologic distribution of the onset of postoperative stroke by surgical approach.

RESULTS

Univariate analysis. The overall mean stroke rate after CABG for the study period from 1996 to 2001 was 2%. The mean yearly stroke rate after off-pump CABG (1.35% [range 0% to 1.64%]) was consistently lower than that for on-pump CABG (2.4% [range 2.3% to 2.95%]) for the period of the study ($p < 0.01$).

The chronologic distribution of stroke was statistically different between the two groups. The median time of the onset of stroke was two days (range 0 to 11) in the on-pump CABG group and four days (range 0 to 14) in the off-pump CABG group ($p < 0.01$) (Fig. 1). The preoperative variables of both groups are presented in Table 1. On univariate analysis, statistical differences were found in the number of grafts, the rate of reoperative CABG, and NNE stroke risk scores (Table 2).

Multivariate analysis. To adjust for potential imbalances in the preoperative risk factors, a multivariate logistic regression analysis was performed. There was no evidence of multicollinearity among the independent variables and no evidence of a lack of fit of the multiple logistic regression model used to test for a difference in preoperative risk factors between surgical approaches. The number of grafts, depressed ejection fraction, and reoperative CABG emerged as independent predictors of postoperative stroke (Table 1). In the 217 patients who had a stroke, postoperative atrial fibrillation occurred in 91 (42%). The median time for stroke occurrence was three days (range 0 to 14 days) for patients who had atrial fibrillation and two days (range 0 to

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Table 1. Baseline Characteristics of Patients After Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery (Univariate Analysis)

	Off-Pump CABG (n = 44)	On-Pump CABG (n = 173)	p Value*
Age category (yrs)			
<70	30 (68%)	96 (55%)	0.58†
70–75	4 (9%)	32 (18%)	
76–79	5 (11%)	37 (21%)	
80+	5 (11%)	8 (5%)	
Female gender	19 (43%)	57 (33%)	0.20
Number of grafts			
1, 2	22 (50%)	13 (8%)	< 0.01†
3, 4	15 (34%)	96 (55%)	
4, 5	6 (14%)	53 (31%)	
>6	1 (6%)	11 (6%)	
Diabetes	18 (41%)	70 (40%)	0.96
Hypertension	38 (86%)	133 (77%)	0.17
Congestive heart failure	6 (14%)	18 (10%)	0.59‡
Recent myocardial infarction	20 (45%)	68 (39%)	0.46
Cerebrovascular accident	4 (9%)	18 (10%)	0.80
Renal failure	2 (5%)	17 (10%)	0.27
COPD	3 (7%)	17 (10%)	0.54
Ejection fraction			
>45%	16 (36%)	46 (27%)	0.12†
35%–45%	9 (30%)	53 (31%)	
25%–34%	4 (32%)	60 (35%)	
<25%	1 (2%)	14 (8%)	
Reoperative CABG	23 (52%)	32 (18%)	< 0.01
NNE stroke risk score (adjusted)	2.8 (0.3–6.5)	2.8 (0.7–6.5)	0.05§
Chronologic distribution of stroke (days)	4 (0–15)	2 (0–11)	< 0.01§

*Chi-square test for general association. †Cochran-Armitage trend test. ‡Fisher exact test. §Wilcoxon rank test. Data are expressed as the number (%) of patients or as the median value (minimum–maximum).

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; NNE = Northern New England.

15 days) for patients without atrial fibrillation ($p = 0.05$, Wilcoxon sign test).

The difference (in quartiles) in the chronologic distribution of stroke between on-pump and off-pump CABG was tested using a cumulative logit model and was statistically significant. The proportional odds assumption was met. The model was adjusted for preoperative risk factors of stroke and also for variables found to be different in the univariate analysis between on-pump and off-pump CABG (NNE stroke risk score, gender, diabetic status, heart failure, recent myocardial infarction, reoperative status, number of vessels grafted, and ejection fraction). Interactions were tested and were not significant. On-pump CABG was associated with a higher risk of early onset of stroke, compared with off-pump CABG (odds ratio 5.3, 95% confidence interval 2.6 to 10.9; $p < 0.01$).

DISCUSSION

Postoperative stroke after on-pump versus off-pump CABG. Coronary artery bypass graft surgery is the single largest cause of iatrogenic stroke in the U.S. (4). The incidence of stroke after on-pump CABG is reported to be between 0.8% and 5.2% (4); thus, we can expect 5,000 to 35,000 new strokes yearly as a result of this procedure (10).

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

	OR (On-Pump CABG)	95% Confidence Interval	p Value
5 or 6 vessels grafted (vs. 1 or 2)	3.9	1.3–14.0	0.02
More than 6 vessels grafted (vs. 1 or 2)	4.7	1.6–15.8	0.01
Ejection fraction 35%–45% (vs. >45%)	3.8	1.4–11.8	0.01
Ejection fraction 25%–34% (vs. >45%)	14.0	3.8–68.6	< 0.001
Ejection fraction <25% (vs. >45%)	17.3	2.4–378	0.02
Previous CABG (vs. first-time CABG)	0.1	0–0.2	< 0.01

Hosmer and Lemeshow goodness-of-fit test: $p^2 = 3.7$, $df = 8$, $p = 0.88$.

CABG = coronary artery bypass graft surgery; OR = odds ratio.

Our investigation documented a lower yearly on-pump stroke rate (2.3% to 2.95%) than that reported in previous studies (3% to 5.6%) (3). Furthermore, our findings support the results of our recent study that the stroke rate after off-pump CABG is lower than the stroke rate after on-pump CABG (5). Off-pump CABG has become increasingly routine over time. At our center, in 1994, only 2% of coronary procedures were done on a beating heart, whereas the respective value for 2001 was 68%.

Mechanisms of stroke after on-pump CABG. Cardiopulmonary bypass is known to cause a systemic inflammatory response and disorders of the coagulation cascade (15,16). Furthermore, prolonged myocardial ischemia, atrial cannulation, aortic manipulation, atrial fibrillation, and the adverse effects of cardioplegia have been implicated as possible contributors to the pathogenic mechanism of postoperative stroke in patients undergoing conventional CABG (2,3,10).

The principal cause of postoperative stroke after on-pump CABG has been suggested to be diffuse microischemia secondary to cerebral microemboli as a result of perfusionist's intervention (air emboli from injections and blood sampling) (17) or from multiple atherosclerotic emboli lodging in brain capillaries (18). Increased capillary permeability and slight postoperative brain edema may also be important corollaries of neurologic dysfunction after on-pump CABG (19).

Mechanism of stroke after off-pump CABG. Possible mechanisms of late-onset stroke after off-pump CABG may include myocardial stunning after off-pump CABG, as previously reported (20). In a previous study, Grubitzsch et al. (20) described two cases of myocardial stunning after off-pump CABG, which they attributed to the temporary myocardial ischemia during off-pump CABG. It is possible that this myocardial stunning may predispose to the occurrence of stroke late in the postoperative course.

Chronologic distribution of stroke after off-pump versus on-pump CABG. In this study, we sought to evaluate the chronologic distribution of the onset of stroke in a cohort of cardiac surgery patients undergoing on-pump CABG versus off-pump CABG. We found that most of the strokes occurred after an initially uncomplicated neurologic recovery from cardiac surgery, echoing previous reports (3).

Our study demonstrated a difference in the chronologic distribution of stroke between off-pump CABG and on-pump CABG. A new finding of this study was that among individuals who had postoperative stroke, patients who had on-pump CABG were at a higher risk of having a stroke earlier in the recovery phase than patients who had off-pump CABG. A multivariate analysis adjusting for potential confounders demonstrated this risk difference between the two surgical approaches. In the present study, the median time of the onset of stroke was two days in the on-pump CABG group versus four days in the off-pump CABG group.

Despite the surgical approach, the percentage of strokes occurring after first awakening from surgery without a neurologic deficit (nearly 73% of all strokes in our study) is similar to that in previous reports, suggesting the number of delayed strokes has not changed in many years (1,3). Ultimately, such morbidity leads to lengthy and costly hospital stays, resulting in resource utilization and subsequent exhaustion of long-term rehabilitation resources.

Clinical implications. Despite the decrease in the risk of thromboembolic events after off-pump CABG compared with on-pump CABG, secondary to elimination of cardiopulmonary bypass, there is a persistent stroke rate associated with it, ranging from 2.1% to 3.1%. The difference in the chronologic distribution of the onset of stroke between off-pump and on-pump CABG-treated patients implies a different mechanism in the pathogenesis of stroke. Embolic phenomena have been previously implicated in the pathophysiology of stroke after on-pump CABG, whereas myocardial stunning may be a mechanism associated with delayed onset of stroke after off-pump CABG (20). The timely administration of platelet inhibitors and/or perioperative anticoagulation may be indicated after off-pump CABG as a preventive measure against delayed onset of stroke. Improvement in surgical strategies, such as the single aortic clamp versus partial occluding clamp technique for the construction of proximal anastomosis, which have been suggested to provide better cerebral protection during CABG, may further decrease the occurrence of postoperative stroke after CABG (21). In our study, this technique was considered but was not standard practice during the study period.

Study limitations. The use of a retrospective methodology was among the limitations of the study, despite the fact that this is the only analysis to relate the surgical approach to the chronologic distribution of stroke. The diagnosis of postoperative stroke was made by an independent neurologist and by computed tomography or magnetic resonance imaging, although a detailed preoperative neurologic assessment was not performed in our patients. There was no postoperative neuropsychological testing that would have enabled the assessment of more subtle neurocognitive impairment, which may represent multiple territory cerebral microinfarcts. Investigation of postoperative predictors of stroke, such as postoperative atrial fibrillation, was outside the scope of our study.

Conclusions. Our results document a difference in the chronologic distribution of stroke for patients undergoing conventional on-pump CABG compared with off-pump CABG, suggesting a different pathophysiologic mechanism for the occurrence of stroke between the two approaches. Conventional on-pump CABG is associated with a stroke onset at an earlier time in the recovery phase, as compared with off-pump CABG. Further studies are necessary to determine what role, if any, operative techniques and/or the timing of anticoagulation therapies play in the pathophys-

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iology and prevention of postoperative stroke in patients undergoing CABG.(11)

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REFERENCES

1. Newman MF, Wolman R, Kanchuger M, et al. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Circulation 1996;94 Suppl II:II74–80.
2. Furlan AJ, Sila CA, Chimowitz MI, Jones SC. Neurologic complications related to cardiac surgery. Neurol Clin 1992;10:145–66.
3. Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. N Engl J Med 1996;335: 1857–63.
4. Hogue CW, Murphy SF, Schechtman KB, Davila-Roman VG. Risk factors for early or delayed stroke after cardiac surgery. Circulation 1999;100:642–7.
5. Stamou SC, Jablonski KA, Pfister AJ, et al. Stroke after conventional versus minimally invasive coronary artery bypass. Ann Thor Surg 2002;74:394–9.
6. Murkin JM, Stump DA. Res ipsa loquitur: protecting the brain in the new millennium, 'outcomes 2000'. Ann Thorac Surg 2000;69:1317–8.
7. Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 2000;69:1162–6.
8. Ricci M, Karamanoukian HL, Abraham R, et al. Stroke in octogenarians undergoing coronary artery surgery with and without cardiopulmonary bypass. Ann Thorac Surg 2000;69:1471–5.
9. Resano F, Stamou SC, Lowery RC, Corso PJ. Coronary artery bypass grafting without cardiopulmonary bypass: anesthetic implications. J Cardiothorac Vasc Anesth 2000;14:1–8.
10. Patel NC, Deodhar AP, Grayson AD, et al. Neurological outcomes in coronary surgery: independent effect of avoiding cardiopulmonary bypass. Ann Thorac Surg 2002;74:400–6.
11. Stamou SC, Hill PC, Dangas G. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. Stroke 2001;32:1508–13.
12. Stamou SC, Pfister AJ, Dangas G, et al. Beating heart versus conventional single-vessel reoperative coronary artery bypass. Ann Thorac Surg 2000;69:1383–7.
13. Wolman R, Nussmeier NA, Aggarwal A, et al. Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. Stroke 1999;30:514–22.
14. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations. Circulation 2002;105:1257–67.
15. Asimakopoulos G. Mechanisms of the systemic inflammatory response. Perfusion 1999;14:269–77.
16. Sablotzki A, Dehne M, Welters I, et al. Alterations of the cytokine network in patients undergoing cardiopulmonary bypass. Perfusion 1997;12:393–403.
17. Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. Ann Thorac Surg 1999;68:89–93.
18. Moody DM, Bell MA, Johnston WE, Prough DS. Brain microemboli during cardiac surgery or aortography. Ann Neurol 1990;28:477–86.
19. Bruer AC, Furlan AJ, Hanson MR, et al. Central nervous system complications of coronary bypass surgery: prospective analysis of 421 patients. Stroke 1983;14:682–7.
20. Grubitzsch H, Ansorge K, Wollert HG, Eckel L. Stunned myocardium after off-pump coronary artery bypass grafting. Ann Thorac Surg 2001;71:352–5.
21. Tsang JC, Morin JF, Tchervenkov CI, Platt RW, Sampalis J, Shum-Tim D. Single aortic clamp versus partial occluding clamp technique for cerebral protection during coronary artery bypass: a randomized prospective trial. J Card Surg 2003;18:158–63.