Risk factors for late stroke after coronary artery bypass grafting

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Background: Postoperative stroke is a severe complication immediately after coronary artery bypass grafting, and it significantly deteriorates the postoperative quality of life if it occurs in the long term. It was the aim of our study to determine factors associated with the occurrence of new strokes during long-term follow-up after coronary artery bypass grafting.

Methods: From 387 of 500 patients undergoing coronary artery bypass grafting (age, 67 years [33-84 years]; 76% male) who had intraoperative epiaortic ultrasonography for assessment of ascending aortic wall thickness, a complete follow-up regarding postoperative stroke was achieved. The median follow-up time was 52 months (9-74 months).

Results: A stroke occurred in 26 (7%) of 387 patients, and the cumulative freedom from stroke was 99%, 95%, and 89% after 1, 3, and 5 years, respectively. A significantly lower freedom from stroke was present in patients with an age of 70 years or more ($P = .007$), preoperative unstable angina ($P = .031$), chronic obstructive pulmonary disease ($P = .009$), carotid artery disease ($P < .001$), preoperative history of neurologic events ($P < .001$), and a maximum ascending aortic wall thickness of 4 mm or more ($P = .010$). Multivariate analysis revealed preoperative history of neurologic events ($P = .021$) to be an independent risk factor.

Conclusion: Patients with ascending aortic atherosclerosis, older age (≥ 70 years), preoperative unstable angina, chronic obstructive pulmonary disease, and carotid artery disease are at risk for late postoperative stroke after coronary artery bypass grafting. A history of neurologic events is of special predictive importance.

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Stroke is one of the leading causes of death in the United States and Europe, and it is one of the most serious complications after coronary artery bypass grafting (CABG). Several risk factors for stroke in the general population are known. On the one hand, nonmodifiable risk factors exist, such as age, male sex, and family history of stroke. On the other hand, some risk factors can be modified by treatment (eg, hypertension, smoking, and hyperlipidemia).¹⁻¹⁷ The occurrence of stroke as a perioperative complication of CABG ranges between 1.1% and 3.8% in the literature. The hospital mortality rate in these patients is as high as 14% to 21%, which is a 10-fold increase compared with that seen in patients undergoing CABG without strokes.¹⁸⁻²³ In the Arterial Revascularization Therapies Study a 1.6% rate

TABLE 1. Preoperative and operative data of 395 patients undergoing epiaortic ultrasonography during CABG and long-term stroke follow-up

Variable	Percentage of patients or median values
Age (y)	67 (33-84)
Male sex	76%
Body mass index	26 (17-37)
Chronic obstructive pulmonary disease	10%
Diabetes mellitus	23%
Hypertension	76%
Increased serum creatinine level (>1.2 mg/dL)	26%
Peripheral vascular disease	16%
Preoperative history of neurologic events	7%
Carotid artery disease	19%
Preoperative unstable angina	20%
Previous cardiac surgery	4%
No. of distal coronary anastomoses	3 (1-5)
Preoperative EuroSCORE	4 (0-18)
Maximum ascending aortic wall thickness ≥ 4 mm	26%

The EuroSCORE is a prediction system of early mortality in patients undergoing cardiac surgery and was applied as described by Nashef and coworkers.²⁶

of cerebrovascular accidents was found at 1 year after CABG.²⁴ Many risk factors for early stroke after CABG have been demonstrated, and we have previously shown that epiaortic ultrasonography can influence the perioperative stroke rate if operative strategies are modified.²⁵ However, less is known about risk factors associated with long-term stroke rates after CABG.

Atherosclerosis of the ascending aorta and the aortic arch is associated with the occurrence of perioperative stroke, and the most sensitive method to detect and quantify ascending aortic atherosclerosis is epiaortic ultrasonography.^{3,7} In a previous study we found that ascending aortic atherosclerosis increases with age and is associated with various pathologies (eg, increased serum creatinine levels, atherosclerosis of the descending aorta, and hypertension).⁵

It was the aim of our study to determine risk factors for late postoperative strokes in patients who underwent ascending aortic evaluation by using epiaortic ultrasonography during CABG.

Patients and Methods

Of 500 hospital survivors who had undergone epiaortic ultrasonography during CABG from 1998 through 2003, follow-up data of 395 patients could be obtained. In a telephone interview the occurrence of postoperative new strokes was collected from the patient or the referring physician. Patients with a perioperative stroke were excluded. Preoperative patient characteristics are shown in Table 1. All patients received aspirin in the hospital postoperatively.

TABLE 2. One-, 3-, and 5-year rates of patients who were free from new stroke after CABG, depending on different risk factors

Factor (no. of patients at risk)	1 y (n = 379)	3 y (n = 313)	5 y (n = 126)
All patients	99%	95%	89%
Age >70 y at operation	99%	91%	79%
Age <70 y at operation	98%	97%	94%
Chronic obstructive pulmonary disease	100%	88%	53%
No chronic obstructive pulmonary disease	98%	96%	91%
Ascending aortic wall ≥ 4 mm	97%	89%	84%
Ascending aortic wall <4 mm	99%	97%	91%
Carotid artery disease	97%	84%	70%
No carotid artery disease	99%	98%	94%
History of neurologic events	96%	65%	65%
No history of neurologic events	99%	97%	91%
Unstable angina before operation	97%	85%	85%
No unstable angina before operation	99%	97%	90%

Definitions

Ascending aortic atherosclerosis was quantified at the time of operation by means of epiaortic ultrasonography in all patients. After sternotomy and opening of the pericardium, the maximum ascending aortic wall thickness was measured with a linear ultrasound probe, as previously described.⁵

Stroke was defined as any neurologic impairment of motor, sensory, or cognitive function that persisted for more than 24 hours or was associated with death and that could not be explained by other neurologic causes (ie, postoperative delirium, dementia, and head trauma).

History of neurologic events was defined as preoperative history of transient ischemic attack or stroke.

Carotid artery disease was defined as the presence of carotid artery stenosis of 50% or more, carotid artery occlusion, or status after carotid endarterectomy. All patients underwent ultrasonography of the carotid arteries preoperatively.

Chronic obstructive pulmonary disease was defined by long-term use of bronchodilators or steroids for lung disease and by significant findings in preoperative spirometry, which was performed in all patients of this series.

Peripheral vascular disease was defined as the presence of intermittent claudication or previous or planned intervention on the abdominal aorta or limb arteries.

Unstable angina was defined according to The Society of Thoracic Surgeons database as follows: rest angina, new onset (<2 months) of Canadian Cardiovascular Society Class (CCSC) III, recent (<2 months) acceleration in pattern and increase of one CCSC class to at least CCSC III, non-Q-wave myocardial infarction, and postinfarction angina (>24 hours).

Hypertension was diagnosed if a systolic blood pressure of greater than 140 mm Hg or a diastolic blood pressure of greater than 90 mm Hg was documented, if the patient was currently

Figure 1. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with an age of 70 years or more.

Figure 3. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with a maximum ascending aortic wall thickness of 4 mm or more.

taking antihypertensive medication, or if the patient had a history of hypertension.

Statistical Analysis

Statistical analysis was carried out with SPSS 10.0 software.

Continuous variables are presented as median (minimum-maximum). Categorical variables are given as percentages. For calculation of freedom from stroke, Kaplan-Meier curves and life tables were used. Factors associated with freedom from stroke were calculated with the log-rank test. A multivariate, stepwise

Cox regression analysis was conducted to determine independent predictors of long-term strokes after CABG. The criterion for a variable entry into multivariate analysis was a univariate probability level of less than .05. A *P* value of <.05 was considered significant.

Results

Moderate-to-severe atherosclerosis with a maximum ascending aortic wall thickness of 4 mm or more, as deter-

Figure 2. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with preoperative unstable angina.

Figure 4. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with chronic obstructive pulmonary disease (COPD).

Figure 5. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with carotid artery disease.

Figure 6. Freedom from stroke of 387 patients undergoing epiaortic ultrasonography during CABG. Note the decreased rate in patients with a preoperative history of neurologic events.

mined at the time of operation by means of epiaortic ultrasonography, was present in 101 (26%) of 387 patients.

During the follow-up period of 52 months (9-74 months), a postoperative new stroke occurred in 26 (7%) of 387 patients. The number of patients at risk was 379, 313, and 126 at 1, 3, and 5 years, respectively. The cumulative freedom from stroke was 99%, 95%, and 89% after 1, 3, and 5 years, respectively (excluding perioperative strokes).

Table 2 shows 1-, 3-, and 5-year rates of freedom from stroke depending on different risk factors.

The following risk factors were significantly associated with a lower freedom from stroke: age of 70 years or more at the time of the operation ($P = .007$, Figure 1), preoperative unstable angina ($P = .031$, Figure 2), maximum ascending aortic wall thickness of 4 mm or more ($P = .010$, Figure 3), chronic obstructive pulmonary disease ($P = .009$, Figure 4), carotid artery disease ($P < .001$, Figure 5), and preoperative history of neurologic events ($P < .001$, Figure 6).

In the multivariate Cox regression model a preoperative history of neurologic events ($P = .021$) was found to be independently associated with a decreased freedom from stroke after CABG (Table 3).

There was no significant association between previous cardiac surgery ($P = .727$), preoperative increased serum creatinine levels of greater than 1.2 mg/dL ($P = .985$), male sex ($P = .594$), hypertension ($P = .472$), diabetes mellitus ($P = .421$), body mass index of less than 30 ($P = .086$), peripheral vascular disease ($P = .057$) and freedom from stroke.

Discussion

Aortic arch atherosclerosis has previously been identified as a risk factor of stroke.¹⁻³ Atherosclerosis of the ascending aorta is associated with a patient's history of neurologic events^{4,5} and with perioperative strokes in patients undergoing cardiac surgery.⁶ In the present study we found ascending aortic atherosclerosis to be associated with the long-term occurrence of stroke after CABG. This is in accordance with findings from Davila-Roman and colleagues,⁷ who showed a freedom from stroke of 82% in patients with severe ascending aortic atherosclerosis at 5 years postoperatively in a mixed cardiac surgery population.

We found an inverse relationship between increased age and freedom from stroke after CABG. This is in agreement with other authors who found an association between age and stroke in the general population.^{8,9} In the Arterial Revascularization Therapies Study increasing age correlated with major adverse cardiac and cerebrovascular events at 1 year after CABG.²⁷ One explanation for this fact might be the increase of risk factors (eg, diabetes mellitus and hypertension aortic atherosclerosis) that accompanies the aging process and progression of cerebrovascular disease.

In our study we found that patients with a history of neurologic events are at higher risk of a postoperative stroke than patients without a history of neurologic events. This is in accordance with the results of other authors, who found that patients who experience a transient ischemic attack or a stroke carry an increased risk of a consecutive (recurrent) stroke.^{10,11}

Interestingly, we found that patients with preoperative unstable angina had a decreased postoperative freedom

from stroke compared with patients without preoperative unstable angina. One pathophysiologic pathway might be the association between inflammatory processes and unstable angina. This can be explained by the evidence of active inflammation with accumulation of macrophages at sites of plaque rupture. Plaque rupture and thrombosis are responsible for about 50% of cases of acute coronary syndromes.^{12,28} On the other hand, chronic inflammation is a major pathologic feature of atherosclerosis, and atherosclerosis is a major cause of stroke.⁹ In addition, Ascione and associates¹⁹ and D'Ancona and coworkers²² found that unstable angina is a risk factor for perioperative stroke after CABG.

In our series patients with carotid artery disease had an increased postoperative occurrence of stroke. This result is comparable with those of other authors, who found that atherosclerotic disease of the carotid arteries is associated with stroke.^{9,13-16} Handa and colleagues¹⁵ found that patients with a high-grade carotid artery stenosis ($\geq 70\%$) had a 21-fold higher risk of stroke than those without such stenosis.

Roach and associates¹⁸ found a more than 2-fold incidence of perioperative neurologic events in patients with pulmonary disease undergoing CABG compared with patients without pulmonary disease. We found chronic obstructive pulmonary disease to be associated with a decreased freedom from late strokes.

Another finding in our study was that patients with peripheral vascular disease had a strong trend toward decreased postoperative freedom from stroke. Rihal and coworkers¹⁷ found a higher rate of neurologic complications immediately after CABG in patients with peripheral vascular disease, but this group included patients with extracranial cerebrovascular disease. Furthermore, Bucerius and associates²¹ identified peripheral vascular disease as an independent predictor of perioperative stroke in patients undergoing cardiac surgery. In a previous study we could demonstrate the association between peripheral vascular disease and ascending aortic atherosclerosis.⁵

Diabetes mellitus is a known risk factor for stroke in the general population.⁹ There are controversial results regarding diabetes as a risk factor of perioperative stroke in patients undergoing CABG, with studies that found diabetes as a risk factor^{22,23} and studies that did not.¹⁹ However, in our series we found no significantly increased stroke rate in patients with diabetes mellitus.

Actually, we also found no association between gender and postoperative stroke rate. Gender as a risk factor for stroke varies in the literature. On the one hand, male gender is a known risk factor of stroke in the general population.⁹ On the other hand, Hogue and coworkers⁶ found female gender to be a risk factor for perioperative stroke in patients undergoing cardiac surgery.

TABLE 3. Factors tested for influence on 5-year freedom from stroke after CABG

Factor	Univariate (log rank)	Multivariate (Cox regression)
Increased serum creatinine level	$P = .985$	Not tested
Previous cardiac surgery (redo)	$P = .727$	Not tested
Hypertension	$P = .472$	Not tested
Male sex	$P = .594$	Not tested
Diabetes mellitus	$P = .421$	Not tested
Body mass index <30	$P = .086$	Not tested
Peripheral vascular disease	$P = .057$	Not tested
Age >70 y at operation	$P = .007$	$P = .328$
Ascending aortic wall ≥ 4 mm	$P = .010$	$P = .187$
Unstable angina before operation	$P = .031$	$P = .075$
Carotid artery disease	$P < .001$	$P = .096$
Chronic obstructive pulmonary disease	$P = .0086$	$P = .068$
History of neurologic events	$P < .001$	$P = .021$

An interesting aspect in all figures is that the divergence of the lines seems to increase at around 24 months. One explanation could be the closer contact to the internist or family doctor earlier after the operation, resulting in detection and treatment of common risk factors of stroke.

For the therapeutic implications of our data, further studies are necessary to find out whether the patients at risk for stroke after CABG might benefit from rigorous treatment of modifiable risk factors (eg, hypertension, smoking, and hyperlipidemia).

In the patients with unstable angina, increased awareness of long-term strokes after CABG is warranted. Early clinical signs have to be taken seriously, and an early diagnosis of inflammatory activity could theoretically be helpful.

Another question is whether oral anticoagulation would be beneficial in patients undergoing CABG with severe ascending aortic atherosclerosis. Studies in a general population of patients with this disease have demonstrated that the long-term freedom from stroke can be reduced if oral anticoagulants are taken.^{29,30}

Our results suggest that ascending aortic atherosclerotic wall thickening, in addition to advanced age (≥ 70 years), carotid artery disease, and chronic obstructive pulmonary disease, is associated with an increased stroke rate during the first postoperative years after CABG. A history of neurologic events is of special predictive importance.

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