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Original research article

Predictors of intracranial cerebral artery stenosis in patients before cardiac surgery and its impact on perioperative and long-term stroke risk



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ABSTRACT

Background: The aim of this prospective study was to determine the prevalence of stenosis within intracranial and extracranial arteries in patients before coronary artery bypass surgery (CABG), to evaluate the influence of intracranial artery stenosis on neurological outcome and to identify preoperative risk factors for these patients.

Methods: One hundred and seventy-five patients (71% males, mean age = 66.1) scheduled for CABG were enrolled for extracranial Doppler duplex sonography, transcranial color-coded duplex sonography (TCCS) and transcranial Doppler (TCD) examination.

Results: Twenty-six patients (14.7%) had extracranial stenosis or occlusion and 13 patients (7.3%) intracranial vascular disease. Six patients (3.5%) had both extra- and intracranial artery disease. The presence of peripheral artery disease and diabetes mellitus was a strong risk factor for extracranial artery stenosis but not for intracranial artery stenosis, which occurred independently also of typical atherosclerotic risk factors like age >70, male sex, hypertension, hyperlipidemia, hyperhomocysteinemia, smoking habit, obesity (BMI > 30) and waist to hip ratio >1. Functional neurological outcome of the patients with intracranial arterial disease evaluated 7 days after CABG was the same as the patients without extra- and intracranial stenosis. However, 12-months neurological follow-up revealed significantly more ischemic strokes in patients with intracranial artery stenosis compared to patients without intracranial stenosis ($p = 0.015$).

Conclusion: The occurrence of intracranial artery stenosis in CABG patients cannot be predicted by well-known atherosclerotic risk factors and seems not to be associated with perioperative stroke.

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Introduction

Stroke is a feared complication of coronary artery bypass graft (CABG) surgery, and despite the improvement in surgical techniques in the last decade, its incidence currently is estimated to be as high as 1.3% to even 4.3% [1]. Cerebral ischemia during the CABG is usually evoked by hypotension–hypoperfusion, embolic phenomena (cardiac or of the aorta), thromboembolism of extracranial and intracranial vessels, or most probably, by the combination of some of these factors [2].

It is well known, that the presence of carotid artery stenosis significantly increases the risk of perioperative stroke and carotid evaluation is currently recommended prior to CABG procedure, although there are still some controversies surrounding prophylactic carotid stenosis management [3]. However, the relevance of intracranial artery stenosis in the group of CABG patients is less clear, mostly because of limitation of available data. In general, intracranial atherosclerosis is believed to be one of the main causes of ischemic stroke and is frequently recognized in the patients with widespread vascular disease. It accounts for about 8–10% of all brain ischemic events. Patients with intracranial stenosis may have a risk of recurrent stroke as high as 20% in the first 2 years despite best medical therapy [4,5].

Thus, we aimed to determine the prevalence of intracranial artery stenosis in patients before elective CABG and to evaluate the influence of intracranial stenosis on perioperative neurological complications and long-time prospective neurological outcome. We also tried to identify predictors for cerebral artery stenosis in CABG patients.

Patients and methods

One hundred and seventy-five consecutive patients scheduled for elective CABG (on the basis of coronary angiography), were enrolled for carotid extracranial Doppler duplex sonography and transcranial color-coded duplex sonography (TCCS) (ESAOTE TECHNOS MPX), and transcranial Doppler (TCD) examination (VIASYS SONARA). Patients without severe coronary artery disease and with no adequate temporal window on TCCS/TCD were excluded from this study.

At each examination, a questionnaire requesting information on demographic background and medical history was completed. Clinical information was obtained directly from the patients and medical records at the time of ultrasound examination. We investigated the presence or absence of hypertension, diabetes mellitus, hyperlipidemia, peripheral artery disease (PAD) and the habit of smoking. Subjects were considered hypertensive if their systolic blood pressure (assessed on repeated measurements) was ≥ 140 mmHg, if their diastolic blood pressure was ≥ 90 mmHg or if they were taking antihypertensive medication. Subjects were defined as diabetic if their fasting glucose level was ≥ 7.00 mmol/L (126 mg/dL) at least twice within a 48 h interval or if they were taking antidiabetic medication. PAD was assessed based on the history of intermittent claudication defined as pain in the muscles of the leg with ambulation. They were classified as smokers if they smoked at least one cigarette per day, as

non-smokers if they had never smoked or smoked shorter than 2 years and quit smoking >1 years prior to examination. Waist circumference was measured around the narrowest point between the coastal margin and the iliac crest. Hip circumference was measured at the level of the widest diameter around the gluteal region. Waist-to-hip ratio (WHR) is waist circumference divided by hip circumference. BMI and WHR were calculated for each subject on the day of ultrasound examination.

The neurological assessment before surgery consisted of an interview and neurological examination. The patients were reevaluated three times – 1 week after surgery (or earlier if necessary), 6 months and 12 months later, and followed by the same neurologist who performed the initial neurological examinations (PL). Development of any case of stroke and the final neurological outcome at discharge were determined (according to NIH Stroke Scale). Stroke was defined as a new and sudden onset of focal neurological deficits lasting >24 h with no apparent nonvascular causes.

The atherosclerotic risk factors were predefined according to the guidelines of the American Heart Association, The Third Joint Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice [6,7] and our University Hospital laboratory's reference values. To investigate the relationship between the number of atherosclerotic risk factors and extracranial or intracranial artery stenosis we classified each patient according to the presence of single or multiple risk factors. Patients were considered to be at risk when one or more of criteria were fulfilled: total cholesterol (T-Chol.) > 200 mg/dL, LDL-C > 135 mg/dL, high density cholesterol (HDL-C) < 40 mg/dL, T-Chol./HDL ratio > 5 , triglycerides > 200 mg/dL, BMI > 30 kg/m² as well as presence of hypertension, diabetes and smoking habits.

The degree of stenosis in the extracranial segment of internal carotid artery (ICA) and vertebral artery (VA) was classified as normal flow or $<50\%$ stenosis, 50–69% stenosis, 70–99% stenosis or occlusion. The degree of stenosis in the intracranial segments of the ICA (iICA) and VA (iVA) as well as the stenosis of the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA) and basilar artery (BA) were classified as normal flow or $<50\%$ or $\geq 50\%$ stenosis or occlusion. The ultrasound examinations were performed by two neurologists (JW and PL, working in consensus). Locations of stenosis were categorized as being in the intracranial or extracranial vessels. The degree of the stenosis was established based on the peak systolic velocity, diastolic velocity and mean flow velocity as previously reported [8,9].

Univariate analyses were performed to assess the association between the prevalence of extracranial artery stenosis (EAS) and intracranial artery stenosis (IAS) with the possible risk factors. First, all variables were analyzed using Fisher's exact χ^2 and Mantel-Haenszel χ^2 tests as appropriate. The t-test was used to compare ages. A multiple logistic regression analysis was used to estimate independent effects of the predictive variables on the cerebral arterial occlusive disease. The analyses were performed separately for extracranial cerebral arteries and intracranial arteries, with each predefined abnormality as a dependent variable and with possible risk factors as independent variables. The level of significance

Table 1 – Demographic data and vascular risk factors of the patients with extracranial artery stenosis (EAS) and intracranial artery stenosis (IAS).

Characteristics	No EAS/No IAS, N = 136	EAS, N = 26	p value	IAS, N = 13	p value
Age (\pm SD)	65.72 \pm 7.2	65.78 \pm 9.0	0.98	70.25 \pm 6.7	0.15
Sex	Male (63.2%)	Male (61.5%)	0.97	Male (61.5%)	0.96
Hypertension	110 (80.9%)	24 (92.3%)	0.76	11 (84.6%)	1.0
Diabetes mellitus	37 (27.2%)	13 (50%)	0.02	2 (18.2%)	0.52
Hyperlipidemia	29 (21.3%)	6 (23.1%)	0.80	2 (18.2%)	1.0
Homocysteine	15.58 \pm 4.1 mmol/l	16.2 \pm 6.2 mmol/l	0.99	12.83 \pm 3.7 mmol/l	0.26
Smoking	35 (25.7%)	10 (38.5%)	0.37	2 (18.2%)	0.52
PAD	23 (16.9%)	12 (46.1%)	0.003	2 (18.2%)	1.0
BMI	28.35 \pm 4.1	28.49 \pm 3.1	0.94	27.85 \pm 3.6	0.97
WHR	0.99 \pm 0.09	0.98 \pm 0.08	0.95	0.969 \pm 0.06	0.825

$p < 0.05$ (bold).

χ^2 test of association, t test or Mann-Whitney test for comparison of means. PAD – peripheral artery disease; BMI – body mass index (m^2/kg); WHR – waist to hip ratio.

was set at $p < 0.05$ for all statistical analyses. The software Statistica 7.0 PL was used to perform all statistical analyses.

Results

The patient group included 127 males and 48 females (mean age, 66.1 \pm 8.6 years, age range 44–85 years). One hundred and thirty-six patients (76.8%) had no hemodynamically significant changes in extra- and intracranial arteries, 26 patients (14.7%) had extracranial stenosis or occlusion and 13 patients (7.3%) presented intracranial vascular disease. Six patients (3.5%) had both extra- and intracranial artery disease.

Demographic data and vascular risk factors of the patients with EAS and IAS are shown in Table 1. Within EAS patients we have found 13 carotid stenoses of 50–69%, 14 carotid stenoses of 70–99%, five cases of carotid occlusion, one vertebral stenosis over 50%, two vertebral occlusions and four cases of subclavian steal syndrome. Half of the EAS patients presented stenosis or occlusion within more than one artery.

Within IAS group three patients had MCA stenosis of more than 50%, two patients had PCA stenosis more than 50%, four patients presented occlusion of intracranial part of VA. We have also noticed two patients with intracranial unilateral

ICA stenosis of more than 50% and two patients with proximal BA stenosis of more than 50%. In total, 22% of all patients presented with hemodynamically important changes in brain supplying arteries.

According to univariate analyses the presence of PAD was a strong risk factor for EAS in patients with severe coronary disease (OR 4.21, 95%CI 1.72–10.27). However, IAS in CABG patients occurred irrespectively of PAD (OR 0.89, 95%CI 0.18–4.30). Similarly, the presence of DM was a risk factor for EAS (OR 2.68, 95%CI 1.14–6.30) but not for IAS (OR 0.49, 95%CI 0.10–2.30).

In our study typical atherosclerotic risk factors like age >70 , male sex, hypertension, hyperlipidemia, hyperhomocysteinemia, smoking habit, obesity (MBI > 30) and WHR > 1 were not significant risk factors neither for EAS nor IAS (Tables 2 and 3).

All patients with carotid stenosis equal or over 70% underwent carotid stenting before CABG. One patient died due to ischemic stroke that occurred just after surgery (non-stenotic group patient). All patients with intracranial stenosis had extremely careful monitoring of blood pressure to avoid brain hypoperfusion. Functional neurological outcome of patients with intracranial arterial disease evaluated 7 days after CABG was the same as the patients without extra- and intracranial stenosis. However, 12-months neurological follow-up revealed

Table 2 – Correlations between coronary artery risk factors and occlusive lesions in extracranial cerebral supplying arteries.

	Odds ratio	95%CI	p value
Age >70 years	1.23	0.43–3.48	0.88
Male sex	0.93	0.32–2.73	0.58
Hypertension	2.83	0.62–12.77	0.25
Diabetes mellitus	2.67	1.14–6.30	0.02
Hyperlipidemia	1.61	0.40–6.45	0.63
Hyperhomocysteinemia	1.07	0.39–2.88	0.99
Smoking	1.80	0.74–4.34	0.23
PAD	4.21	1.72–10.27	0.003
BMI > 30	0.76	0.21–2.78	0.99
WHR > 1	1.19	0.47–2.97	0.81

$p < 0.05$ (bold).

PAD – peripheral artery disease; BMI – body mass index (m^2/kg); WHR – waist to hip ratio.

Table 3 – Correlations between coronary artery risk factors and occlusive lesions in intracranial cerebral supplying arteries.

	Odds ratio	95%CI	p value
Age >70 years	1.74	0.53–5.65	0.35
Male sex	1.20	0.31–4.6	1.0
Hypertension	1.3	0.27–6.22	1.0
Diabetes mellitus	0.49	0.10–2.30	0.52
Hyperlipidemia	0.67	0.14–3.20	1.0
Hyperhomocysteinemia	0.69	0.19–2.40	0.52
Smoking	0.52	0.11–2.49	0.52
PAD	0.89	0.18–4.30	1.0
BMI > 30	0.72	0.16–3.14	0.72
WHR > 1	0.48	0.10–2.37	0.46

PAD – peripheral artery disease; BMI – body mass index (m^2/kg); WHR – waist to hip ratio.

significantly more ischemic strokes in patients with IAS (three events) compared to patients without intracranial stenosis (one event) (OR 17.6, 95%CI 1.75-176.69) ($p = 0.015$).

Discussion

Perioperative neurological injuries (stroke as well as cognitive dysfunction) seem to be the most devastating complications of CABG [1,10]. Stroke is classically characterized as a neurological deficit attributed to an acute focal cerebral, spinal or retinal injury of a vascular origin, including cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke is the most common type observed in CABG patients, however perioperative procedures sometimes provoke brain hemorrhage [11]. Clinical symptoms of stroke usually consist of dysphasia (inability to speak and understand), one-side paresis, sensation disturbance, vision field deficit or ataxia. Stroke is associated with the prolonged hospitalization, altered quality of life and increased hospital mortality [1,12]. In one study perioperative CABG stroke determined a four-fold higher chance of death [13].

Previous studies have described numerous risk factors of neurologic complications during CABG, for example, chronic renal failure, previous stroke, advanced age, female gender, impaired left ventricular function, carotid disease, diabetes mellitus and atherosclerosis of the ascending aorta [14-16]. The current study suggests that the majority of strokes that occur during CABG are caused by cerebral macroemboli and/or cerebral hypoperfusion [11,17]. Possible sources of cerebral macroemboli during CABG may be the carotid arteries, ascending aorta, intracerebral arteries or intracardiac cavities. Cerebral hypoperfusion is mostly seen in carotid artery disease patients and may lead to stroke in watershed regions of brain [18]. On CT or MRI scans watershed strokes appear as an area of hypodensity between the middle and anterior cerebral artery or the middle and posterior cerebral artery supplying territory.

The recent recommendations for carotid evaluation before CABG suggest that carotid duplex ultrasonography should be performed in patients with at least one of the following features: age over 65, left main coronary stenosis, PAD, prior transient ischemic attack (TIA) or stroke and carotid bruit [3]. However, there is lack of high quality evidence to guide decision making about revascularization in patients undergoing CABG, and available guidelines are based on limited data in this area of clinical practice [19]. Carotid revascularization is recommended in patients scheduled for CABG when carotid stenosis is symptomatic or bilateral [20,21]. Unilateral asymptomatic carotid stenosis management before CABG is still unsolved [19].

Cerebral perfusion pressure (CPP) is the key pressure gradient causing blood brain perfusion (blood flow to the brain). It should be maintained over 60 mmHg to prevent inadequate blood flow and in consequence brain ischemia [22]. CPP is related to mean systemic blood pressure (MBP) and intracranial pressure (ICP) [$CPP = MBP - ICP$]. ICP is almost constant value and reaches up to 10-15 mmHg. Thus, based on definition, CPP mostly relates to MBP. Under normal circumstances (MBP between 70 and 150 mmHg and ICP about 10 mmHg), average cerebral blood flow is relatively constant

due to cerebral vessel autoregulation. Additionally, proper blood supply to the hypoperfused regions of brain may be preserved by net of collateral flow. Carotid stenosis place CABG patients at higher risk of stroke due to the hypoperfusion or embolization from carotid plaque or both of them, especially in patients with poor brain collateral flow. Gold et al. found fewer neurological complications after CABG surgery when mean arterial pressure during procedure was between 80 and 100 mmHg rather than between 50 and 60 mmHg [23]. Reduced cerebral blood flow during surgery might be a primary cause of ischemic brain injury, or it could exacerbate injury by impairing clearance of microembolisms [24].

In our center we recommend carotid revascularization in all patients before CABG if stenosis is over 70% as a routine practice. Carotid stenting is a favorable method as it is described as safer procedure for hemodynamically unstable patients [3]. The results of our study showed that 14.7% patients presented with extracranial artery stenosis or occlusion. According to univariate analyses PAD and DM were strong risk factor for EAS. In our study typical atherosclerotic risk factors like age >70, male sex, hypertension, hyperlipidemia, hyperhomocysteinemia, smoking habit, obesity (BMI > 30) and WHR > 1 were not significant predictors of EAS in patients scheduled for CABG. Similar results were reported previously, as in studies performed by Alkan et al. [25] and Uehara et al. [26].

The intracranial vascular atherosclerosis is one of the major causes of ischemic stroke. It is believed that it accounts for about 10% of all brain ischemic episodes. The presence of IAS brings a 20% risk of recurrent stroke in the first few years [4,5]. Ischemic stroke may result from hypoperfusion distally to the site of stenosis or occlusion of the artery in case of acute thrombosis. Moreover atheromatic plaque may close small penetrating arteries (especially branches of MCA) and may be the source of embolic material itself [25,27]. Intracranial atherosclerotic stenosis is typically located within infraclinoid portion of ICA and within the MCA, VA and BA. Intracranial artery flow evaluation before cardiac surgery is not a routine practice and most patients are limited only to extracranial artery examination. In this study we used Doppler Duplex ultrasound examination to evaluate neck vessels as well as intracranial brain circulation. Our study showed that in contrast to extracranial occlusive lesions the presence of IAS in CABG patients was not predicted by any of the evaluated typical atheromatic risk factors.

The previous studies noted that compared to EAS, IAS does not correlate as well with the known atherosclerotic risk factors for coronary and peripheral vascular disease (i.e., male sex, age, hypercholesterolemia). Bae et al. (2006) suggests that the correlation between coronary atherosclerosis and extracranial artery stenosis is stronger than that between coronary atherosclerosis and intracranial artery stenosis [28]. Similarly, peripheral vascular disease correlates stronger with extracranial stenosis than intracranial stenosis. However, IAS is commonly associated with certain races and geographic variables (black race, Japanese and Chinese are more prone to IAS). Similarly to Alkan et al., we did not find any correlations between the presence of intracranial occlusive disease and incidence of typical risk factors [25]. Alternatively, novel risk factors for atherosclerosis should be investigated.

In our study, after the surgery we observed one severe ischemic stroke caused by total occlusion of proximal segment of MCA (no-EAS, no-IAS group patient). Seven days after the CABG, neurological examination (assessed according to NIHSS scale) did not reveal any new neurological dysfunction in the rest of the patients. However, 12-month follow up of all patients revealed significant difference in stroke occurrence between intracranial stenotic group (three ischemic strokes) and non-stenotic group (one ischemic stroke). The same neurological outcome of the patients with intracranial stenosis and the patients without intracranial vessel pathology shortly after surgery was surprising, but may be partially explained by extremely careful monitoring of the IAS patients during intraoperative and postoperative period (especially for avoiding hypotension). Further, in contrast to non-stenotic group, the intracranial stenosis group was treated with dual antiplatelet therapy for 3 months after the surgery, what may be beneficial for this group of patients [29]. Such treatment could make some biases between the groups but was recommended in our center from initiation of the study. At present, short-time (up to 90 days) dual antiplatelet therapy with clopidogrel and aspirin is recommended in intracranial stenotic patients with TIA/stroke [30]. We strongly believe that use of dual antiplatelet therapy may be an effective strategy to further reduce the risk of stroke in patients with intracranial artery stenosis scheduled for CABG, but not for all populations. Large observational study is required to address this question.

Conclusions

A sizeable proportion of patients undergoing CABG surgery was found to have extracranial and/or intracranial artery disease. Our study showed that the presence of IAS does not affect neurological outcome shortly after the cardiac surgery, however it was a significant risk factor for ischemic stroke during the 1-year follow up. The lack of acute strokes during the perioperative period in IAS patients may have partially resulted from very careful hemodynamic monitoring during the CABG surgery and within the next days. Despite the fact that we did not find any significant correlation between the presence of IAS and stroke occurrence during CABG surgery, it seems reasonable to categorize such patients into a higher risk group. Since TCD examination can evaluate the cerebral flow and indicate the patients with poor cerebral perfusion reserve, we recommend this examination in all patients scheduled for elective CABG.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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