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Association of periprocedural neurological deficit in carotid stenting with increased anticardiolipin antibodies

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ABSTRACT

Introduction: Carotid stenting (CS) has become a therapeutic alternative to endarterectomy in selected patients. Periinterventional plaque thromboembolism leading to neurological ischemic events remain the major risk of the procedure. We prospectively studied the potential role of thrombophilic conditions including anticardiolipin antibodies (ACA, IgG and IgM isotype), lupus anticoagulants, activated protein C resistance, antithrombin, and protein C and S.

Material and Methods: The study was approved by the local ethics committee, and written informed consent was obtained from all patients. In total, 236 consecutive patients were included (158 men, 78 woman; median age 73 years). Prothrombotic markers were quantitated on the day of admission. Periprocedural neurological deficits (PND) occurring within 48 hours of the intervention were recorded and classified by an independent neurologist as transient ischemic attack, minor or major stroke. Uni- and multivariable logistic regression analysis were performed to test for the influence of thrombophilic conditions, demographic factors and lesion characteristics on PND.

Results: Neurologic complications occurred in 18 interventions (7.6%). In 4 (36.4%; 3 minor, 1major stroke) out of 11 patients with elevated IgG-ACA neurological events were observed as compared to 14 (6.2%; 6 TIA, 5 minor stroke, 3 major stroke) out of 225 patients with normal IgG-ACA levels. In multivariable analysis, two variables were independently associated with PND: elevated IgG-ACA (OR 6.09, 95% CI 1.49-25.88; $P=0.012$) and lesion length >10 mm (OR 4.36, 95% CI 1.19 to 16.01; $P=0.027$).

Conclusions: A thrombophilic condition due to elevation of anticardiolipin antibodies increases the risk of periinterventional neurological complications during CS.

Introduction

In cerebrovascular disease (CVD) the role of various thrombophilic conditions as an independent risk factor for stroke is still controversial. Several studies indicated a positive association of anticardiolipin antibodies and lupus anticoagulant (LA) with stroke in patient subgroups [1–3]. A potential association of antithrombin [4,5], protein C [6,7] or protein S [8] deficiency with ischemic stroke was also described in case reports and small studies. Similarily, the relationship between activated Protein C resistance (APCR) and cerebral arterial thrombosis is still indistinct [9–14].

As we are unaware of studies investigating a potential association of thrombogenic factors and periprocedural stroke risk during carotid interventions we designed a prospective trial to investigate ACA, LA, antithrombin, protein C and S deficiencies, and APCR in patients undergoing protected and unprotected carotid artery stenting.

Material and Methods

Study Population

The protocol was approved by the local Ethics Review Committee and written informed consent was obtained from all study participants.

Two hundred thirty-six consecutive patients undergoing CS as therapy for high-grade internal carotid artery stenosis were prospectively enrolled in the study from June 1999 to December 2003. Patients, in whom a second intervention for contralateral stenosis was performed, were included only for the first intervention. In total, 236

Abbreviations: CS, Carotid stenting; ACA, anticardiolipin antibodies; PND, Periprocedural neurological deficits; CVD, cerebrovascular disease; TIA, transient ischemic attack; LA, lupus anticoagulant; APCR, activated Protein C resistance; ICA, internal carotid artery; CCT, cranial computed tomography; AT, antithrombin; P C, protein C; P S, protein S; ACT, activated clotting time; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

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Table 1
Baseline Characteristics in Patients with and without PND (n = 236).

	PND (n = 18)	No PND (n = 218)	*P*
Age, y	76 (71-80)	73 (63-77)	0.076
Age ≥80 y, n(%)	6 (33.3)	38 (17.4)	0.096
Female, n(%)	6 (33.3)	72 (33)	0.979
Symptomatic CVD within last 6 months, n(%)	6 (33.3)	57 (26.2)	0.51
History of TIA or stroke, n(%)	8 (44.4)	77 (35.3)	0.438
Contralateral ICA occlusion, n(%)	3 (16.7)	17 (7.8)	0.193
Contralateral ICA stenosis ≥50%, n(%)	8 (44.4)	77 (35.3)	0.505
Coronary Artery Disease, n(%)	9 (50)	110 (50.5)	0.97
Peripheral Artery Disease, n(%)	6 (33.3)	90 (41.3)	0.509
Obesity (BMI >30 kg/m^2), n(%)	4 (22.2)	49 (22.4)	1.0
Hypertension, n(%)	16 (88.9)	178 (81.7)	0.44
Diabetes, n(%)	9 (50)	72 (33)	0.145
Hypercholesterolemia, n(%)	17 (94.4)	187 (85.8)	0.302
Smoking within last 6 months, n(%)	3 (16.7)	48 (22)	0.77

TIA indicates transient ischemic attack; CVD, cerebrovascular disease; ICA, internal carotid artery; BMI, body mass index. Continuous data are shown as median (interquartile range) and analyzed using Mann Whitney U test. Dichotomous data are shown as n(%) and analyzed using the Chi square test or the Fisher exact test where appropriate.

carotid interventions were performed for symptomatic (n = 63) or asymptomatic (n = 173) carotid stenosis. Symptomatic CVD was defined as any sign of neurologic ischemic deficit within the last six months. Neurological examination was performed routinely by an independent neurologist in each patient before and after intervention. Indication for the procedure was ≥70% stenosis of the extracranial internal carotid artery (ICA) in symptomatic patients or ≥80% stenosis of the ICA in asymptomatic patients with one of the following criteria: rapid progression during the last 12 months, contra-lateral ICA occlusion, CS required preoperatively (e.g. preceding coronary bypass grafting), clinically silent cerebral infarction on cranial computed tomography (CCT) scans consistent with thromboembolism from the carotid plaque. The degree of stenosis was estimated according to duplex ultrasound velocity criteria [15] and clinical indication for intervention was obtained from an independent neurologist. The final decision to treat was based on the angiographic degree of stenosis (according to the North American Symptomatic Carotid Endarterectomy Trial) using the distal ICA diameter as reference segment [16]. Periinterventional neurological deficit was examined and classified by an independent neurologist. Baseline CCT was mandatory in all patients to exclude an intracranial tumor or cerebral hemorrhage.

Exclusion criteria for enrollment in the study comprised of malignant tumors, infectious diseases, known connective tissue diseases or severe renal insufficiency (creatinin >2 mg/dl).

Laboratory Tests

Baseline blood studies prior to intervention included complete blood count, lipoprotein profile, serum creatinin and parameters of inflammation (C-reactive protein, fibrinogen). Prothrombin fragment F1.2 levels was measured by enzyme-linked immunosorbent assay (Enzygnost® F1.2 micro, Dade Behring, Germany). Resistance to activated protein C (APC-R; COA Test® APC Resistance, Chromogenix, Milan, Italy), antithrombin (AT; STA Antithrombin, Diagnostica Stago, Asnieres, France), protein C (P C; COAMATIC® Protein C, Chromogenix), protein S (P S; STA Protein S clotting, Diagnostica Stago), were determined fully automated (STA compact analyzer, Diagnostica Stago) with following reference ranges: APC resistance ratio >1.9; AT activity 70-120%; P C activity 70-140%; P S activity 60-140%. All patients with APC-R ≤1.9 were genotyped for factor V Leiden mutation. Determination of the factor V Leiden mutation was carried out by standard procedures with a multiplexed mutagenically separated polymerase chain reaction assay (MS PCR) as previously described using genomic DNA isolated from citrated blood [17]. The presence of anticardiolipin antibodies was determined by commercially available kits (Varelisa Cardiolipin IgG Antibodies and Varelisa Cardiolipin IgM Antibodies, Pharmacia Diagnostics, Freiburg, Germany). IgG isotype titers >15 units/ml (U/ml) and IgM isotype titers >10 units/mL were considered positive. Both assays are based on the principle of ELISA with cardiolipin coated polystyrol plates and ß$_2$-glycoprotein as a cofactor for anti-cardiolipin antibodies added within the sample buffer.

The presence of lupus anticoagulant was established according to current criteria for the diagnosis of LA [18]. Confirmation studies included the LA confirm (DRVVT) test (Gradipore, North Ryde, Australia) and STACLOT® LA (Diagnostica Stago).

Balloon Angioplasty and Stenting Protocol

Antiplatelet therapy consisted of aspirin (100 mg/day) for at least seven days and clopidogrel (75 mg/day; 4× 75 mg loading dose on day one) for at least two days prior to intervention. Since the routine use of cerebral protection during CS was implemented during our trial, the last 86 interventions were performed using distal filter protection devices.

Three operators with various levels of interventional experience performed the procedures. A detailed description of the interventional technique has been published elsewhere [19]. Briefly, after transfemoral vascular access 5000 units unfractionated heparin were administered. Patients with an activated clotting time (ACT) <250 seconds received a second heparin bolus (30 Units/kg). Cerebral angiography was performed in at least two planes using a 5-french sidewinder diagnostic catheter selectively placed in the left and right common carotid artery. After documentation of length and grade of the lesion the guidewire was navigated through the stenosis and predilatation was performed using a 3-3.5/30 mm rapid exchange (Rx) balloon catheter. Selfexpanding stents (Wallstent: Boston Scientific; Acculink-stent: Guidant) were deployed in all patients either unprotected over the wire or protected in monorail technique with distal filter device (FilterWire EX: Boston Scientific; AccuNet: Guidant). Stent deployment was followed by dilation within the stent using a 5- or 6-mm-diameter balloon and a pressure of 8-10 atm for 5 seconds. After stent placement, selective control angiography was performed to evaluate local result and examine the intracranial arteries. The vascular access sheath was removed immediately after intervention and the puncture site was sealed with Angioseal (St. Jude Medical).

Table 2
Carotid Lesion Characteristics (n = 236).

	PND (n = 18)	No PND (n = 218)	*P*
Left sided lesion, n(%)	5 (27.8)	100 (45.9)	0.12
Location of stenosis, n(%)			
Within ICA, not involving the ostium	5 (27.8)	68 (31.2)	
Within ICA, involving the ostium	6 (33.3)	106 (48.6)	0.657*
Bifurcational lesion	7 (38.9)	44 (20.2)	0.203*
Morphology, n(%)			
No or minor irregularities	8 (44.4)	104 (47.7)	
Major irregularities	10 (55.6)	1114 (52.3)	0.783
Calcification	7 (38.9)	106 (48.6)	0.715
Degree of stenosis, %	84 (70.4–88)	83 (78-90)	0.478
Lesion length, mm	12.9 (11.7-22.1)	9.8 (6.1-14.4)	0.010
Extended lesion length >10 mm, n(%)	15 (83.3)	98 (45)	0.003
Procedural Data			
Use of protection device, n(%)	6 (33.3)	80 (36.7)	0.776
Residual stenosis, %	10 (0-13)	10 (0-18)	0.704

ICA indicates internal carotid artery; Continuous data are shown as median (interquartile range) and analyzed using Mann Whitney U test. Dichotomous data are shown as n(%) and analyzed using the Chi square test or the Fisher exact test where appropriate. *Compared to stenosis within ICA.