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ORIGINAL RESEARCH

Preprocedural C-Reactive Protein Levels Predict Stroke and Death in Patients Undergoing Carotid Stenting

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BACKGROUND AND PURPOSE: Elevated baseline levels of C-reactive protein (CRP) are associated with an adverse outcome during coronary stent placement. The aim of this study was to evaluate whether preprocedural CRP levels also are predictive of stroke and death in patients undergoing carotid stent placement (CAS).

MATERIALS AND METHODS: We reviewed data prospectively collected from 130 patients (97 men, 33 women; mean age, 68.5 ± 10.1 years; range, 43–89 years) who underwent CAS for symptomatic carotid stenosis and from whom preprocedural CRP values had been obtained. A CRP value of >5 mg/L was considered to be elevated. The frequency of stroke and death within 30 days was compared between patients with and without elevated baseline CRP levels using χ^2 and multivariate logistic regression analysis.

RESULTS: Baseline CRP values were normal in 94 (72.3%) patients but were elevated in 36 (27.7%) patients. The demographic and clinical characteristics were similar in both treatment groups. The 30-day stroke and death rate was significantly higher in patients with elevated CRP values (8/36; 22.2%) than in those without (3/94; 3.2%; $P < .01$). After adjusting for demographic characteristics, degree of carotid stenosis, and use of cerebral protection devices and/or statin therapy, an elevated CRP value before CAS remained a significant and independent predictor of stroke and death within 30 days after CAS (odds ratio, 7.7; 95% confidence interval: 1.8–32.8, $P = .006$).

CONCLUSIONS: Baseline CRP is a powerful predictor of outcome in patients undergoing CAS, which underscores the role of inflammation in the pathogenesis of embolic complications during this procedure.

During the past decade, increasing evidence has indicated that inflammation plays an important role in the initiation and progression of atherosclerotic disease involving both coronary and carotid arteries.[1,2] C-reactive protein (CRP), serum amyloid A protein, and fibrinogen are acute phase reactants that are synthesized in response to proinflammatory cytokines. Among these, CRP is the most common systemic marker of inflammation. In patients with substantial carotid artery narrowing, elevated CRP levels have been observed in those with recent cerebral ischemic symptoms,[3] indicating that inflammation not only is part of the atherosclerotic process but also may indicate the clinical course. In support of this notion, serum CRP concentrations have recently been shown to be a marker for unstable carotid plaque.[4] Because of the high risk of recurrent stroke in patients with a recently symptomatic carotid stenosis, several landmark studies have been performed to unequivocally demonstrate that carotid endarterectomy (CEA) effectively reduces this risk.[5,6] Along with CEA, carotid angioplasty and stent placement (CAS) is increasingly being used as a therapeutic alternative. Although several recent randomized trials and large, single-center studies have indicated that CAS can be performed with acceptable periprocedural complication rates,[7-10] distal embolization of plaque fragments to the brain is one of the major limitations of this method and is probably associated with the plaque stability. Although a number of recent studies have demonstrated an association between baseline CRP values and adverse outcome during coronary stent placement,[11-14] little is known about the utility of this inflammatory marker for prediction of ischemic events in patients treated with CAS. Therefore, we sought to investigate whether elevated preprocedural CRP levels are associated with an increased risk of stroke or death within 30 days in patients undergoing CAS for symptomatic carotid stenosis.

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Materials and Methods

Study Population

Prospectively collected data were reviewed for all patients with high-grade symptomatic carotid stenosis (≥70% assessed with sonography according to European Carotid Surgery Trial [ECST] criteria[6]); patients were treated with CAS at 2 university hospitals (Tübingen and Göttingen) between January 2000 and December 2005. A carotid stenosis was considered symptomatic if the patient had experienced an ipsilateral ocular or cerebral (permanent or transient) ischemic event within the past 6 months. All patients were informed of the investigative nature of CAS and gave their written consent. The Institutional Ethics Review Board of both universities approved the CAS protocol. The outcomes of patients treated at the university hospital of Tübingen and various subgroup analyses have been published previously.[9,15,16]

Carotid Stent Protocol

All patients were treated with carotid angioplasty with stent placement according to a standardized protocol recently described in de-

tail.[9] At first, all CAS procedures had been performed without cerebral protection devices. When cerebral protection devices became available, the choice of which type of device to use, if any, depended on the personal preference of the interventional neuroradiologist performing the procedure. At least 3 days before the procedure, patients received orally administered aspirin (100 mg daily) and clopidogrel (75 mg daily). Clopidogrel was continued for a 6-week period, and aspirin was given indefinitely. To document patency of the stent, all patients routinely received a sonography at the follow-up visit 1–2 days after CAS.

Data Collection and Clinical Evaluation

A stroke neurologist obtained the medical history of and performed neurologic examination on each patient before CAS. Additional neurologic examinations were performed the day after CAS and at day 30. The following cerebrovascular risk factors were recorded using history or direct measurements: hypertension (blood pressure ≥140/90 mmHg, based on the established World Health Organization criteria and measured on repeated occasions), diabetes mellitus (Hb_{A1c} >6.5%, fasting blood glucose >120 mg/dL, or presence of antidiabetic drugs), hyperlipidemia (fasting serum cholesterol levels >220 mg/dL or presence of lipid-lowering drugs), smoking (current or within the previous year), previous transient ischemic attacks and strokes, coronary artery disease (angina, myocardial infarction, percutaneous transluminal angioplasty, or surgery), and the presence of contralateral carotid disease (assessed with sonography). To exclude a current pulmonary or urinary tract infection, all patients received chest radiographs and a urinary analysis.

C-Reactive Protein Measurements

In both hospitals, peripheral blood samples were assayed within 24 hours before CAS with a routine test for CRP (Rolf Greiner BioChemica, Germany or Advia 1650 Chemistry System; Bayer Diagnostics, Germany). Both tests used an immunoprecipitation technique of serum CRP with photometric analysis. The elevated preprocedural CRP level was defined as >5 mg/L, the upper normal reference value in both laboratories.

Definitions of Clinical Outcome Measures

The clinical outcome measures were minor or major stroke or death within 30 days and were defined as follows[17]:

Minor Stroke. Any new neurologic deficit (either ocular or cerebral) that persisted for more than 24 hours and that either resolved completely within 30 days or increased the National Institutes of Health stroke scale score by ≤3 points.

Major Stroke. Any new neurologic deficit that persisted after 30 days or increased the National Institutes of Health stroke scale score by >3 points.

Statistical Analysis

Continuous values were expressed as mean ± SD and nominal variables as counts and percentages. For comparisons of categorical data, 2-tailed χ^2 statistics with Yates correction and univariate Fisher exact test were used. The Fisher exact test was used when the predicted contingency table cell values were less than 5. Analyses of continuous variables between the cohorts were performed with an unpaired Student *t* test. A multiple logistic regression analysis was applied to assess the independent effect of preprocedural CRP values on postinterventional complication rates, whereas adjustment was performed for the potentially confounding effects of other baseline variables. Baseline variables were considered for inclusion in this analysis if they were imbalanced between both treatment groups, which were indicated by a *P* value of less than .2. Moreover, variables that were likely to influence the incidence of cardiovascular events (eg, the degree of carotid stenosis, the use of cerebral protection devices during CAS, the type of the stent, or the year in which the intervention was performed) were entered into this analysis. Interaction was assessed using additive and multiplicative interaction terms. Results of the logistic regression model are presented as odds ratio (OR) and 95% confidence interval (CI). A *P* value of less than .05 was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (version 13; SPSS, Chicago, Ill).

Table 1: Baseline characteristics of patients with and without available CRP values

	With CRP (n = 130)	Without CRP (n = 148)	*P* Values
Mean age (years)	68.5 (±10.1)	69.1 (±8.9)	.583
Age >80 years	10 (13%)	18 (12.2%)	.237
Male	97 (74.6%)	96 (64.9%)	.116
Hypertension	102 (78.5%)	123 (83.1%)	.279
Hyperlipidemia	68 (52.3%)	79 (53.4%)	.904
Current tobacco use	41 (31.5%)	36 (24.3%)	.282
Diabetes mellitus	35 (26.9%)	38 (25.7%)	1.0
Coronary artery disease	29 (22.3%)	46 (31.1%)	.170
Contralateral ICA occlusion	14 (10.8%)	11 (7.4%)	.211
Contralateral ICA stenosis (≥50%)	25 (19.2%)	28 (18.9%)	1.0

Note:—CRP indicates C-reactive protein; ICA, internal carotid artery.

Results

From January 2000 to December 2005, a total of 278 consecutive patients with a symptomatic carotid stenosis had been treated with CAS at both institutions. Of these patients, preprocedural CRP values had been obtained in 130 patients (97 men and 33 women; mean age, 68.5 ± 10.1 years; age range, 43–89 years) who comprised the study population for this analysis. The remaining 148 patients were excluded; of these, 18 patients either had confounding disease states (eg, such as inflammatory, neoplastic, or infectious diseases) or factors leading to elevated CRP levels (eg, treatment with steroids, immunosuppressive drugs, or nonsteroidal anti-inflammatory drugs, except for low-dose aspirin or clopidogrel), and 130 patients did not have CRP values. With respect to the baseline characteristics, there were no significant differences between the population of patients with available CRP values and those without (Table 1).

Thirty-six (27.7%) patients had elevated CRP values before CAS. The demographic and clinical characteristics of patients with normal preprocedural CRP values and those with elevated CRP values before CAS were similar; however, there were more male patients in the group with elevated CRP values than in the group with normal CRP levels (Table 2). Hypertension and hyperlipidemia were the most frequent vascular risk factors in both groups, followed by cigarette smoking, diabetes mellitus, and coronary artery disease.

CAS was successful in all patients, and patency of the reconstructed artery was documented with a sonography follow-up study in each patient. Table 3 summarizes the postprocedural complication rates within 30 days. For the entire study population, the minor stroke rate was 7 of 130 (5.38%), the

Table 2: Patient characteristics according to preprocedural CRP levels*

	Normal CRP	Elevated CRP†	*P* Value
Demographic			
n	94 (72.3%)	36 (27.7%)	
Mean age (years)	67.9 (±10.3)	69.9 (±9.7)	.330
Age >80 years	5 (5.3%)	5 (13.9%)	.139
Male	65 (69.1%)	32 (88.9%)	.024
Presentation			
Stroke	43 (45.7%)	18 (50.0%)	.698
Hemispherical TIA	37 (39.4%)	15 (41.7%)	.843
Retinal TIA	14 (14.9%)	3 (8.3%)	.396
Symptom onset to CAS (days)	21.7 (±18.4)	25.3 (±28.3)	.529
Medical conditions			
Hypertension	72 (76.6%)	30 (83.3%)	.481
Hyperlipidemia	50 (53.2%)	18 (50.0%)	.845
Current tobacco use	31 (32.0%)	10 (27.8%)	.675
Diabetes mellitus	22 (23.4%)	13 (36.1%)	.185
Coronary artery disease	21 (22.3%)	8 (22.2%)	1.0
Radiological conditions			
Carotid artery stenosis right	41 (43.6%)	20 (55.6%)	.331
Degree of stenosis (%)	89.3 (±6.2)	87.8 (±8.9)	.297
Contralateral ICA occlusion	8 (8.5%)	6 (16.7%)	.210
Contralateral ICA stenosis (≥50%)	20 (21.3%)	5 (13.9%)	.458
Carotid protection	24 (27.0%)	8 (25%)	1.0
Current medication			
Statins	30 (31.9%)	14 (38.9%)	.535
Angiotensin-converting enzyme inhibitors	39 (41.9%)	18 (50.0%)	.432
β-Adrenergic receptor blockers	25 (26.6%)	8 (22.2%)	.660
Diuretics	23 (24.5%)	14 (38.9%)	.129
Serum parameters			
Cholesterol (mg/dL)	205 (±49.5)	195.2 (±44.6)	.292
Triglyceride (mg/dL)	179.9 (±134.6)	189.7 (±106.2)	.726
LDL (mg/dL)	138.0 (±39.9)	132.6 (±32.5)	.649
HDL (mg/dL)	47.8 (±13.6)	43.2 (±8.2)	.254
CRP (mg/L)	0.7 (±1.5)	12.9 (±11.6)	.001

Note:—CAS indicates carotid artery stent; CRP, C-reactive protein, HDL, high-density lipoprotein; ICA, internal carotid artery; LDL, low-density lipoprotein; TIA, transient ischemic attack.
* Data are mean values ± SD or n (%).
† Elevated CRP values refer to >5 mg/L.

Table 3: Periprocedural complications within 30 days after CAS according to preprocedural CRP levels

	Normal CRP ($n = 94$)	Elevated CRP ($n = 36$)	*P* Value*
Minor stroke	2 (2.1%)	5 (13.9%)	.0174
Major stroke	1 (1.1%)	1 (2.8%)	.4787
Death	0 (0%)	2 (5.6%)	.0751
Any stroke or death	3 (3.2%)	8 (22.2%)	.0015

Note:—CRP indicates C-reactive protein.
* *P* values are from χ^2 analysis.

major stroke rate was 2 of 130 (1.54%), and the death rate was 2 of 130 (1.54%). All strokes were ipsilateral to the treated artery and occurred either during or within 24 hours after CAS.

The incidence of stroke and death within 30 days was significantly different ($P < .01$) between patients with elevated preprocedural CRP values (22.2%) and those with normal CRP values (3.2%) (Table 3). In a multivariate logistic regression model, after adjusting for all the significant univariate predictors and for statin therapy, baseline CRP (OR, 7.7; 95% CI, 1.8–32.8, $P = .006$) and age >80 years (OR, 8.8; 95% CI, 1.7–44.9, $P = .009$) remained significant independent predictors of stroke and death after CAS.

Discussion

In this study, we analyzed the relationship between baseline CRP levels and cardiovascular complications after CAS in patients with a symptomatic carotid stenosis. Our results suggest that elevated preprocedural CRP levels are associated with an increased risk of stroke and death after CAS in these patients. To the best of our knowledge, a similar finding has not been reported before. Whereas several recent clinical studies have revealed an association between the extent of myocardial injury during percutaneous coronary interventions and baseline CRP values,[11-14] our study supports the notion preprocedural levels of acute-phase reactants also are clinically relevant predictors of outcome during carotid interventions. The relationship between elevated baseline CRP and ischemic complications during and after CAS was independent of other possible confounders, including concomitant statin therapy, which has been shown to reduce CRP levels.[18]

Because all ischemic adverse events occurred either during or within the first hours after CAS, it is likely that the poorer outcome among patients with a high CRP level is a consequence of a greater thrombotic hazard. At least indirectly, this assumption is supported by a recent observation of an increased microembolization during CAS in patients with high preprocedural leukocyte counts,[19] which are subsequently significantly correlated with CRP.[20]

Several mechanisms could account for an increased risk of thrombotic events after CAS in patients with elevated preprocedural CRP levels. Ligand-bound or aggregated human CRP is a potent activator of the complement cascade, unleashing various proinflammatory mediators, which have been associated with direct damage of endothelial cells, enhancement of clotting by induction of tissue factor expression, and the formation of procoagulant microvesicles.[21,22] In addition, CRP may cause human monocytes to synthesize tissue factor, a potent procoagulant.[23] Finally, CRP also contributes to endothelial dysfunction and induces expression of cell adhesion molecules.[24] Thus, with respect to possible mechanisms linking CRP to thromboembolic complications during CAS, CRP may be related to pathologic substrates, such as the diffuseness of disease and friability of the atheromatous lesion that predispose to microembolization or to the propensity of clot formation at the site of angioplasty-induced arterial injury.

This study has strengths but also several important limitations. Although we used the data from our prospective CAS series, the potential influence of preprocedural CRP values on cardiovascular complications after CAS was analyzed in a retrospective fashion. Therefore, our results must be confirmed in further prospective trials. At first, CRP values had not been obtained systematically in all patients, and neither high-sensitivity CRP testing nor repeated or serial measurements were performed. Conversely, the combined 30-day stroke and death rates within our entire CAS series did not differ between patients with (8.5%) and without (8.1%; data not shown) CRP values, indicating that selection bias did not play a major role in our findings. Finally, although we tried to control for baseline imbalances between patients with normal CRP values and

those with elevated CRP levels, the possibility of residual or undetected confounding variables cannot be ruled out completely.

In conclusion, elevated serum CRP levels are associated with a less favorable prognosis in patients with a symptomatic carotid stenosis who undergo CAS. Our results suggest that the measurement of CRP at baseline may help to identify those who are at an increased risk of adverse ischemic events. Although future prospective studies are warranted to corroborate this relationship, these patients may benefit from a treatment strategy aimed at attenuating the systemic inflammation.

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