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Elevated C-Reactive Protein Is Associated with an Increased Intima to Media Thickness of the Common Carotid Artery

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Key Words
Intima to media thickness · C-reactive protein · Duplex sonography · Atherosclerosis · Chronic inflammation

Abstract
In this study, we analyzed the relationship between serum C-reactive protein (CRP) and the intima to media thickness (IMT) of the common carotid artery in 411 consecutive neurological inpatients (215 males, mean age 64.1 years). The CRP concentration was determined within 12 h and patients were subdivided according to the CRP level. Patients with an elevated CRP (n = 149) showed a significantly larger IMT [1.05 mm (95% confidence interval (CI) 1.02–1.09) vs. 0.92 mm (95% CI 0.89–0.94)]. Multivariate linear regression analysis revealed that an elevated CRP level, age, pack-years of smoking, body mass index, incidence of diabetes mellitus and ischemic stroke were independently associated with an increased IMT ($p < 0.05$).

Introduction

Elevated levels of C-reactive protein (CRP), a sensitive marker of systemic inflammation, appear to predict cardiovascular events such as stroke and myocardial infarction among apparently healthy individuals [1–4]. Moreover, elevated CRP levels are associated with an increased risk of recurrent infarction or death [5]. However, the role of CRP in the pathogenesis of atherosclerosis has not yet been unequivocally clarified. In normal human coronary arteries, no CRP-specific immunoreactivity could be found [6]. The grade of immunoreactivity of CRP has been found to be positively correlated with the size of coronary plaques, as well as the coronary intima to media wall thickness (IMT) [6]. The use of B-mode real-time ultrasound offers the opportunity to assess the IMT of the common carotid artery (CCA) as a suitable marker for subclinical atherosclerosis [7–9]. A large prospective multicenter study identified the IMT as a strong predictor of stroke and myocardial infarction in healthy adults over 65 years of age [10]. Nevertheless, the impact of CRP on carotid IMT in patients with and without cerebrovascular disease has not yet been studied in detail. As CRP levels appear to be a marker for subclinical chronic inflammation [11], it was the aim of our study to analyze the asso-

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Table 1. Demographic data, cardiovascular risk factors and baseline laboratory parameters of the patients with (CRP ≥0.5 mg/dl) and without (CRP <0.5 mg/dl) increased CRP concentration

	CRP <0.5 mg/dl	CRP ≥0.5 mg/dl	p values
Patients	262	149	
Age, years	63 (61–64)	67 (65–69)	0.001
Sex (male/female)	129/133	86/63	NS
Hypertension	141 (54%)	110 (74%)	<0.0001
Ischemic stroke	131 (50%)	101 (68%)	<0.0001
IHD	51 (20%)	45 (30%)	0.013
Hypercholesterolemia	119 (45%)	84 (56%)	0.033
Plaques	125 (48%)	95 (64%)	0.002
Carotid artery stenosis			
None	222 (85%)	122 (82%)	NS
Moderate	24 (9%)	15 (11%)	NS
Severe	16 (6%)	12 (8%)	NS
Pack-years of smoking	10.7 (8.3–13.0)	16.1 (12.0–20.2)	0.024
HbA1c, %	5.4 (5.4–5.6)	6.0 (5.3–6.7)	NS
Cholesterol, mmol/l	6.06 (5.9–6.24)	5.88 (5.64–6.08)	NS
HDL, mmol/l	1.43 (1.35–1.51)	1.25 (1.17–1.33)	0.001
Triglyceride, mmol/l	1.71 (1.53–1.89)	1.8 (1.60–2.05)	NS
LDL, mmol/l	3.9 (3.78–4.08)	3.87 (3.67–4.11)	NS
BMI	24.1 (23.4–24.7)	25.5 (24.7–26.4)	0.004
IMT, mm	0.92 (0.89–0.94)	1.05 (1.02–1.09)	<0.0001
Adjusted IMT[1], mm	0.92 (0.92–0.93)	0.98 (0.97–0.99)	<0.0001

Values in parentheses represent 95% CIs, except where otherwise indicated. NS = Not significant.

[1] IMT adjusted for other possible risk factors (age, BMI, hypertension, hypercholesterolemia, pack-years of smoking, incidence of ischemic stroke, carotid plaques and IHD).

ciation between CRP levels determined within 12 h (initial CRP) and the IMT of the CCA in a large number of consecutive neurological inpatients.

Patients and Methods

Patients

Four hundred and fifty-six consecutive neurological inpatients (214 males; mean age 64.1 years, 95% confidence interval (CI) 62.7–65.5 years) hospitalized for the first time because of a cerebral ischemic event [transient ischemic attack (n = 59) or ischemic stroke (n = 151)] or other neurological disorders [Parkinson's disease (n = 23), dementia (n = 11), vertigo (n = 13), syncope (n = 12), chronic pain (n = 24), myasthenia gravis (n = 5), intracerebral bleeding (n = 28), polyneuropathy (n = 12), movement disorders (n = 17), dystonia (n = 7), seizures (n = 17), multiple sclerosis (n = 9), headache (n = 13), normal pressure hydrocephalus (n = 4) and myopathy (n = 6)] were studied. The initial CRP level, other laboratory parameters such as total cholesterol, triglycerides and HbA1c and cardiovascular risk factors such as body mass index (BMI), pack-years of smoking, hypercholesterolemia (treatment with cholesterol-lowering drugs or a total cholesterol level ≥240 mg/dl), incidence of arterial hypertension (treatment with antihypertensive medication or documented blood pressure ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic), diabetes mellitus (treatment with antidiabetic drugs or diagnosis of diabetes during hospital stay), cerebral ischemic events, ischemic heart disease (IHD; documented by previous myocardial infarction or angina pectoris, bypass surgery or >50% angiographic stenosis of ≥1 major coronary artery), carotid artery stenosis and carotid plaques were determined. According to the CRP level, patients were subdivided into two groups: normal CRP (<0.5 mg/dl, n = 262) and elevated CRP (≥0.5 mg/dl, n = 149) (table 1). To further analyze the association between CRP and IMT with regard to cerebrovascular disease, patients were also subdivided according to cerebrovascular events.

Cholesterol Measurement

After overnight fasting, a blood sample was drawn and the lipids were measured by our laboratory. The cholesterol was measured on a Hitachi 747 analyzer (Roche Diagnostics, Mannheim, Germany) using original reagent kits. The determination is based on an enzymatic cleavage of cholesterol esters by cholesterol esterase at 37°C followed by an oxidation step catalyzed by cholesterol oxidase. Measuring range is from 3 to 800 mg/ml.

CRP Measurement

In all stroke patients (n = 210), the CRP concentration was measured within 12 h after symptom onset, and in patients without a cerebral ischemic event, the CRP concentration was measured with-

in 12 h after admission. The CRP was determined in a serum specimen using a Dimension® RxL clinical chemistry analyzer with CRP Flex™ reagent cartridges. Latex particles coated with antibody to CRP aggregate in the presence of CRP in the serum sample. The increase in turbidity (measured at 340 nm), which accompanies aggregation, is proportional to the actual CRP concentration. The assay range was 0.2–12 mg/dl. A concentration ≥0.5 mg/dl was defined as elevated according to the reference values of our laboratory. The intraassay variability of the test is 4.2% at 0.7 mg/ml and the interassay variability is 7.1% at 0.7 mg/ml.

Carotid Artery Measurements

Duplex ultrasonography was performed by an investigator blinded to the CRP measurement, using a 7.5-MHz linear array transducer (Acuson 128 XP10, USA). Both internal carotid arteries were defined as normal, or having plaques (1–29% reduction), moderate stenosis (30–70% reduction) or severe stenosis (>70% reduction) according to the European Carotid Surgery Trial criteria [12]. The measurement of CCA IMT was done according to the methods of the Atherosclerosis Risk in Communities study [13–15]. An optimal longitudinal image was saved and the IMT was analyzed using a computerized image analysis system (SigmaScan Pro, Jandel, USA) off-line. IMT measurements were performed 0.8–1.8 cm proximal to the tip of the flow divider at the far wall of the CCA because of the more clearly defined boundaries there [16]. In this segment, the IMT was measured five times every 2 mm. The mean IMT was defined as the average across the left and the right side. The reproducibility of the CCA IMT measurement using duplex ultrasonography has been demonstrated in several studies [13–15, 17, 18]. For the computerized image analysis used in our study, reproducibility of the IMT measurements with a Spearman correlation coefficient ranging from 0.82 to 0.86 was described recently [19].

Statistical Analysis

All values are given as the mean and 95% CI. Independent t tests were used to test for differences between both subgroups. Because the distribution of CRP was highly skewed, the CRP levels were natural log transformed. Adjustment for multiple comparisons was done using the Bonferroni method. The variation of the IMT between the subgroups according to gender, age, BMI, pack-years of smoking, cholesterol, log CRP, incidence of plaques, stroke, IHD and hypertension was tested with an analysis of covariance (ANCOVA) using SYSTAT (SPSS Inc., USA). The covariate-adjusted means were calculated using this software. Multivariate linear regression analysis was performed using forward selection followed by backward elimination of covariates, resulting in an equation where only covariates that significantly increase the predictability of the dependent variable are included. All covariates were tested for interactions with each other. The IMT was defined as the dependent variable. Age, BMI, pack-years of smoking, cholesterol, log CRP, gender and the incidence of hypertension, cerebral ischemic events, IHD and diabetes were defined as independent variables. The IMT data were entered as continuous values in the model. A p value <0.05 was considered statistically significant. The observed adjusted IMT values (minimum = 0.72 mm, maximum 1.12 mm) were equally subdivided into quartiles. Additionally, we determined the prevalence of an elevated CRP within increasing IMT quartiles. For this analysis, the IMT was adjusted for age, pack-years of smoking, BMI, incidence of hypertension, ischemic stroke, IHD, diabetes and hypercholesterolemia.

Results

From the 456 consecutive inpatients, 411 (215 males; mean age 64.1 years, 95% CI 62.7–65.5 years) were enrolled in this study. Forty-five patients were excluded because of (1) acute or recently treated infections or disease-related CRP elevation (n = 32) or (2) missing CRP data within the first 12 h after symptom onset/hospitalization (n = 14). The mean CRP level was 0.69 mg/dl (95% CI 0.64–0.73) and ranged from 0.2 to 3.7 mg/dl. We found no significant differences in the CRP concentration at the different times of measurement (i.e. 0–3, 3–6 and 6–12 h after symptom onset). No significant differences for gender, triglycerides, LDL cholesterol, total cholesterol and incidence of diabetes mellitus were observed between the subgroups with normal and elevated CRP (table 1). Patients with increased CRP levels on admission (≥0.5 mg/dl) showed a significantly increased CCA IMT (fig. 1, table 1). In addition, BMI, age, incidence of ischemic stroke, arterial hypertension and IHD were significantly elevated. These patients also showed lower HDL cholesterol and more pack-years of smoking (table 1). The association between elevated CRP levels and increased IMT remains nearly unchanged after adjustment for the other risk factors using an ANCOVA model. To evaluate the influence of the different risk factors on IMT, a stepwise multivariate linear regression analysis was performed. This analysis revealed six independent factors that were significantly correlated with IMT (table 2). None of the other tested risk factors significantly increased the predictability of the regression. The predicted model accounted jointly for 28% of the variation in IMT. From the 411 inpatients included, 210 were hospitalized because of a cerebrovascular ischemic event. To analyze the effect of CRP on cerebrovascular disease, the patients were subdivided according to this parameter. In addition to an increased incidence of several known cardiovascular risk factors, including the CCA IMT, a significantly elevated CRP was observed in the stroke group (table 3). Patients with increased CRP levels showed significantly increased IMT values in both subgroups as compared to patients with normal CRP (fig. 1). No significant difference in IMT was found between patients with and without stroke and elevated CRP levels (fig. 1), whereas stroke patients with normal CRP showed significantly larger IMT values as compared to patients without stroke and normal CRP. The prevalence of elevated CRP levels within increasing IMT quartiles is given in figure 2. We observed the most increased prevalence for an elevated CRP in the highest IMT quartile.

Table 2. Determinants of CCA IMT

	Coefficient	Standardized partial regression coefficient	p value
Age	0.006 (0.004–0.008)	0.383	<0.0001
Pack-years of smoking	0.002 (0.0019–0.002)	0.188	<0.0001
Cerebral ischemic events	0.027 (0.007–0.047)	0.117	<0.05
BMI	0.008 (0.002–0.014)	0.108	<0.05
Diabetes mellitus	0.024 (–0.005–0.053)	0.077	<0.05
Log CRP	0.042 (–0.001–0.085)	0.084	<0.05
Multiple R^2		0.28	<0.0001

Values in parentheses represent the 95% CIs. The coefficient gives estimates for how much the dependent variable (IMT) will change if the respective variable is increased by 1 and the other variables were held constant. The standardized partial regression coefficient gives the coefficients that would be obtained if all variables were standardized. If there were just one predictor, then this parameter would be its correlation with the dependent variable.

Table 3. Demographic data, cardiovascular risk factors and baseline laboratory parameters of the patients with and without acute or former cerebral ischemic events (including transient ischemic attack and ischemic stroke)

	Ischemic event		p values
	yes	no	
Patients	210	201	
Age, years	65 (63–67)	59 (57–62)	<0.0001
Sex (male/female)	116/94	106/95	NS
Hypertension	157 (75%)	72 (36%)	<0.0001
IHD	71 (34%)	10 (5%)	<0.0001
Hypercholesterolemia	94 (48%)	55 (27%)	<0.0001
Plaques	118 (56%)	64 (32%)	<0.0001
Carotid artery stenosis			
None	166 (79%)	195 (97%)	<0.0001
Moderate	27 (13%)	3 (1%)	<0.0001
Severe	17 (8%)	3 (1%)	0.002
Pack-years of smoking	19.5 (16.0–22.9)	8.1 (5.9–10.2)	<0.0001
HbA1c, %	5.8 (5.7–5.9)	5.4 (5.4–5.5)	<0.0001
Cholesterol, mmol/l	6.01 (5.80–6.23)	5.98 (5.77–6.16)	NS
HDL, mmol/l	1.33 (1.27–1.40)	1.43 (1.33–1.53)	NS
Triglyceride, mmol/l	1.82 (1.65–2.07)	1.63 (1.53–1.74)	NS
LDL, mmol/l	3.64 (3.48–3.82)	4.06 (3.74–4.37)	NS
CRP, mg/dl	0.64 (0.59–0.69)	0.52 (0.50–0.54)	<0.0001
Log CRP, mg/dl	–0.61 (–0.58 to –0.65)	–0.697 (–0.67 to –0.71)	0.002
BMI	24.1 (23.3–24.9)	23.6 (22.8–24.4)	NS
IMT, mm	0.98 (0.95–1.02)	0.87 (0.84–0.89)	<0.0001
Adjusted IMT[1], mm	0.97 (0.96–0.98)	0.89 (0.88–0.89)	<0.0001

Values in parentheses represent 95% CIs, except where otherwise indicated. NS = Not significant.

[1] IMT adjusted for other possible risk factors (age, BMI, hypertension, hypercholesterolemia, pack-years of smoking, incidence of carotid plaques and IHD).

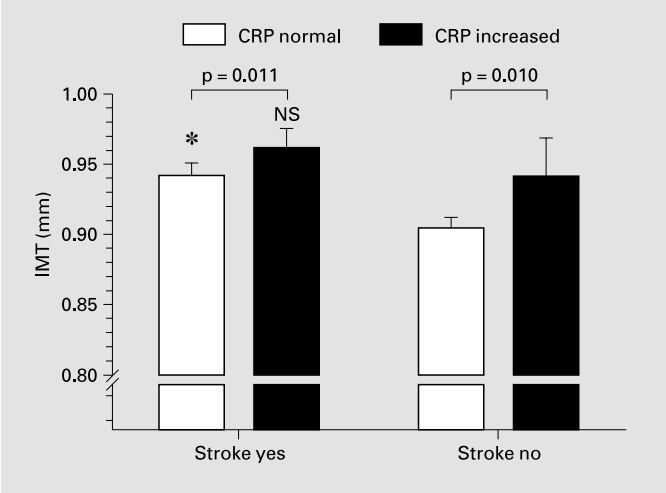

Fig. 1. Relationship between IMT (adjusted for age, hypertension, hypercholesterolemia and IHD) and CRP in patients with and without cerebrovascular ischemic events. NS = Not significant compared to patients with increased CRP levels and no history of cerebrovascular ischemic events. * $p < 0.001$ compared to patients with normal CRP levels and no history of cerebrovascular ischemic events.

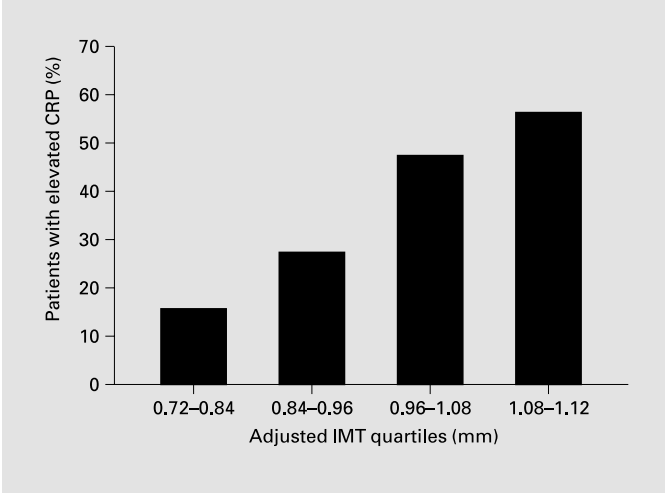

Fig. 2. Prevalence of elevated CRP levels within increasing IMT quartiles (adjusted for age, BMI, pack-years of smoking, incidence of hypertension, IHD, stroke and hypercholesterolemia).

Discussion

Our study demonstrates that an increased initial serum CRP concentration determined within 12 h after stroke onset or admission (nonstroke patients) was associated with an increased IMT of the CCA in a large number of patients with and without cerebrovascular disease. A multivariate linear regression analysis revealed that the CRP represents an independent predictor for intimal thickening. These results cannot be explained in terms of established risk factors for cardiovascular disease, because the association remains nearly unchanged after adjustment for several other indices of disease risk. Hak et al. [20] described a weak association between CRP and IMT of the CCA in healthy middle-aged women, which was, however, limited to ever-smokers. Two limitations of our study should be discussed. Firstly, one could argue that our results may be influenced by a selection bias concerning the patient population because the measurements were performed on an inpatient basis. However, we found comparable risk factors for an increased IMT to those in other population-based studies, i.e. age, BMI, pack-years of smoking, incidence of diabetes and stroke [10, 13, 21–24]. Previous investigators found hypertension to be either associated [25–27] or not associated [28, 29] with carotid atherosclerosis. Additionally, Sander et al. [19] and Sander and Klingelhöfer [25] described the daytime blood pressure variability rather than the absolute blood pressure values as the strongest predictor of early carotid atherosclerosis and progression of IMT. In contrast to other studies [13, 30, 31], hypercholesterolemia was not independently associated with IMT in the present study. This might be explained by the fact that the subjects were younger in the other studies and the incidence of ischemic stroke, hypertension and IHD was lower. Furthermore, we included the incidence of stroke and IHD in the linear regression analysis. Moreover, a treatment effect might explain the differences between our investigation and population-based studies, as most of our inpatients were already being treated with antihypertensive and lipid-lowering drugs. Secondly, the study was not prospectively designed to assess the CRP development in patients with ischemic stroke and patients without ischemic stroke. Therefore, we could not completely exclude the possibility that any acute-phase response following brain ischemia is differently expressed in patients with and without increased IMT. However, we could not find a significant difference regarding the CRP concentration measured 0–3, 3–6 or 6–12 h after stroke onset. Liuzzo et al. [32] demonstrated that the CRP peak after myocardial infarction occurs at 48 h or later. Because of these findings, we propose that the CRP concentration measured within 12 h after stroke symptom onset is not influenced by any acute-phase response. Up to now, it was an issue of debate whether the relationship between CRP and cardiovascu-

lar disease was due to inflammation of the vascular wall because of chronic infection or inflammation originating in a more remote site, with secondary effects on the vascular wall through cytokines and other mediators [33, 34]. Recently, Zhang et al. [6] demonstrated the existence of CRP in human coronary arteries and observed a positive correlation between increased coronary IMT and the grade of CRP immunoreactivity. Yudkin et al. [35] hypothesize that a low-level chronic inflammatory state may induce endothelial dysfunction leading to cardiovascular diseases. An association between chronic inflammation and the early stages of carotid atherosclerosis was supported by our data concerning the close relationship between CRP levels and IMT measured by high-resolution B-mode ultrasonography. However, to define more exactly the role of the CRP level in the development of subclinical atherosclerosis, particularly in asymptomatic patients with no other cardiovascular risk factors, a prospective study is needed. We observed an association between CRP and IMT in patients with, as well as without, a history of cerebrovascular ischemic events. In both subgroups, patients with elevated CRP levels showed significantly increased IMT values as compared to patients with normal CRP. Interestingly, no significant difference in IMT was found between patients with and without stroke and elevated CRP levels. In contrast, patients with normal CRP levels and cerebrovascular disease showed a larger IMT than patients without a history of a cerebrovascular event and normal CRP. One could argue that the increased IMT in the subgroups of patients with and without stroke might be due to a different expression of wall modifications, i.e. media layer for increased CRP without stroke and intimal layer for the stroke subgroups. However, to the best of our knowledge, it is not possible using duplex ultrasonography to reliably differentiate between the media layer and the intimal layer of the CCA. The importance of the CRP level has also been supported in studies with clinical end points. Tracy et al. [36] reported that the CRP level was associated with incident events in healthy elderly subjects, especially in those with subclinical disease at baseline. Furthermore, in apparently healthy postmenopausal women, the CRP concentration was the strongest predictor for the risk of cardiovascular events over a mean follow-up of 3 years [4].

The IMT was recently described as a strong predictor of both myocardial infarction and stroke even after adjustment for other risk factors and is associated with several cardiovascular risk factors [30, 37], the prevalence of cardiovascular disease [30, 37, 38] and general atherosclerosis [13, 39]. The association between IMT and outcome was at least as strong as the association seen with traditional risk factors [10]. Based on our findings, we consider that a combination of carotid IMT and baseline CRP measurements may help to identify patients with a high-risk profile for future cardiovascular events, particularly in asymptomatic subjects.

In conclusion, our data showed that an elevated initial CRP was independently associated with increased IMT of the CCA in a large number of consecutive patients with and without a history of a cerebrovascular ischemic events and a different cerebrovascular risk pattern and may support the importance of inflammation even in the early stages of atherosclerosis development.

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