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Is Serum Pregnancy-Associated Plasma Protein A Really a Potential Marker of Atherosclerotic Carotid Plaque Stability?

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Abstract *Objectives:* The search for markers predicting risk of plaque rupture in carotid atherosclerosis is still ongoing. Previous findings showed that pregnancy-associated plasma protein-A (PAPP-A) levels correlate with an adverse plaque morphology. However, the role of PAPP-A in plaque destabilisation is still uncertain.
Material and methods: Patients with carotid artery stenosis involved in the study were asymptomatic ($n = 29$) and symptomatic ($n = 37$). Carotid plaques were characterised by histology ($n = 33$). Immunohistochemistry ($n = 17$) was used to determine expression of PAPP-A and CD68 within the plaques. Serum levels of PAPP-A were measured by the enzyme-linked immunosorbent assay (ELISA).
Results: Circulating PAPP-A levels were significantly higher in patients with unstable versus stable plaques (0.10 ± 0.06 vs. 0.07 ± 0.04 $\mu g\,ml^{-1}$, $p = 0.047$) and interestingly, in asymptomatic versus symptomatic patients (0.11 ± 0.05 vs. 0.069 ± 0.09 $\mu g\,ml^{-1}$, $p = 0.025$). These differences remained statistically significant after adjustment for age, gender and degree of stenosis ($p = 0.050$). PAPP-A expression in plaques correlated significantly with CD68 positive macrophages, cap-thickness and its serological values ($r = +0.291$, $p < 0.001$, $r = -0.639$, $p < 0.001$ and $r = 0.618$, $p < 0.008$, respectively). Furthermore, PAPP-A serum values demonstrated a significant positive predictive value of 68.8% for unstable plaques.

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Conclusion: Our present data confirmed the close relationship between expression of PAPP-A and plaque instability and furthermore correlated significantly with cap thickness. However, the question whether PAPP-A is a useful predictive marker of plaque instability remains unresolved.

Ischaemic strokes are commonly caused by a cerebral embolus originating from formation of a platelet-rich thrombus superimposed on atherosclerotic plaque or by plaque rupture in the carotid artery. Conventional risk factors often fail to identify patients with rupture-prone plaques at high risk of an impending stroke. It has been recognised that plaque properties other than size and degree of stenosis are important for the identification of patients at high risk of cerebral ischaemic events. This applies in particular to unstable plaques.[1] New concepts on pathophysiology of plaque vulnerability and rupture have been recently established and have contributed to a better understanding of the molecular and cellular mechanisms involved.[2] New markers of atherosclerotic plaque development and activity are believed to identify patients at high risk of impending stroke among which the pregnancy-associated plasma protein A (PAPP-A) is an interesting candidate.[3] Recently, peripheral blood levels of PAPP-A have been proposed as a possible biological marker of acute coronary syndromes.[4] Furthermore, some biochemical and imaging studies have revealed PAPP-A as a factor that may reflect a high risk of vulnerability.[3,4] For example, Bayes-Genis demonstrated a correlation between plasma concentration and plaque stability in coronary arteries. We hypothesised that PAPP-A may be also involved in the transformation from a stable to an unstable plaque in carotid artery stenosis (CS).

In our study, we therefore examined circulating blood levels of PAPP-A in patients with symptomatic and asymptomatic carotid artery stenosis. Furthermore, we evaluated the relationships between circulating PAPP-A, expression of PAPP-A in the diseased carotid artery and plaque stability.

Material and Methods

Patient population

The groups of this prospective study consisted of 29 consecutive patients with high-degree asymptomatic carotid artery stenosis (mean $\pm$ SD age, 67.9 $\pm$ 8.2 years, male 21, female eight), and 37 consecutive patients with clinically symptomatic carotid artery stenosis (mean $\pm$ SD age, 68.1 $\pm$ 8.6 years, male 25, female 12) scheduled for carotid thrombendarterectomy (Table 1). Stenosis was evaluated by colour-coded duplex sonography following.

European Carotid Surgery Trial (ECST) criteria.[5] Stenosis was considered as symptomatic if the patient had experienced an ipsilateral ocular or cerebral (permanent or transient) ischaemic event within 6 weeks prior to endarterectomy. Carotid endarterectomies were performed by experienced surgeons during a 9-month period. All patients underwent detailed neurological examination within 2 days before operation to discriminate between asymptomatic and symptomatic carotid artery disease.

Table 1 Presentation of the numbers of patients.

	Asymptomatic pat.	Symptomatic pat.	Total
Serology	29	37	66
Histology	15	18	33
ICH	9	8	17

All patients with severe carotid artery stenosis (>70% in asymptomatic and 60% in symptomatic patients) according to recent American Heart Association (AHA) Recommendations and a complete three-dimensional plaque suitable for histological examination after the surgical procedure were included in the study.

Exclusion criteria included any kind of acute infectious diseases within the last 6 weeks, advanced liver or kidney failure, myocardial infarction, unstable or chronic stable, effort-induced angina of at least 6 months duration accompanied by evidence of severe coronary artery disease, cardiac catheter intervention and history of major trauma and cardiac or general surgery and peripheral arterial occlusive disease (rest pain or gangrene) within the last 6 months.

The study was performed according to the Guidelines of the World Medical Association Declaration of Helsinki and written and informed consent was obtained from all patients. The study was approved by the Review Board Committee of the Interdisciplinary Center for Vascular Diseases of the Technical University of Munich.

Laboratory analysis

Blood samples were obtained at the time of admission to the vascular surgery unit from an antecubital vein. All samples were analysed according to the results of Pai, who investigated the stability of novel plasma markers at different time points from specimen collection until processing.[6] Blood serum samples of each patient were frozen within 2 h after collection.

PAPP-A levels in plasma were determined by means of a solid phase enzyme-linked immunosorbent assay (ELISA; Biosource Europe, Nivelles, France) based on the sandwich principle with analytical sensitivity of $<0.19\ \mu g\ ml^{-1}$ and intra-assay/interassay coefficients of variation of 4.08% and 6.39%, respectively. This kit uses a microplate with wells coated with polyclonal anti-PAPP-A antibody.

An ELISA reader (Dynatech Laboratories, USA) set to 450 nm with wavelength correction set to 620 nm determined optical density. All standard biochemistry measurements were carried out by the Biochemistry Department at our institution using standard methods.

Histology/immunohistochemistry

For histological analyses and immunohistochemistry (IHC), 33 patients (15 asymptomatic and 18 symptomatic) and 17

patients (nine asymptomatic and eight symptomatic) were included, respectively.

Carotid plaques were removed *en bloc* during surgery to preserve the entire plaque structure. Plaques were subsequently cut into serial cross sections, starting at the site of the bifurcation area up to the end of the stenosis. A representative section for further analysis was defined as the area with the highest degree of lumen stenosis. Within this area, four consecutive sections were taken for analysis from each patients' sample to avoid accidental results.

IHC was performed on sections (2–3 μm) of formalin-fixed and paraffin-embedded plaque–tissue samples. Paraffin sections were first dewaxed with xylene and rehydrated in descending ethanol sequence (100–70%). Plaque tissue sections were then routinely stained with haematoxylin and eosin (HE) and Elastin van Gieson (EvG) to assess tissue structure of all plaque samples, cellular composition, degree of infiltration with inflammatory cells, plaque rupture, intraplaque haemorrhage, atheroma-associated foam cells and atheroma-associated macrophages. For IHC, dewaxed and hydrated tissue section samples were treated with boiling to retrieve epitopes of appropriate antigens, washed and treated with appropriate antibodies (PAPP-A, polyclonal rabbit anti-human, dilution 1:200, anti-CD68, clone KP1, dilution 1:2000, Dako, Hamburg, Germany) to characterise cellular components of cross sections and to detect expression of PAPP-A.

An experienced pathologist blinded to sample identity and symptoms graded cross sections for histological features associated with plaque vulnerability. Histological characterisation of stable and unstable plaques was performed based on the already-established and published methods of the modified AHA scheme.[7] Colocalisation studies for macrophage foam-cells were performed at serial sections using antibodies against CD68 antigen and PAPP-A. A quantitative analysis was performed by measuring areas of PAPP-A-positive cells in relation to areas of CD68-positive cells as well as to the total cross section area. SigmaScan 4.0 (Systat Software Inc., San Jose, USA) was used for measurement of areas of expression. Final data were then calculated as areas of PAPP-expression − plaque area − ratio (% of plaque area in mm^2).

Statistical analysis

Values of continuous variables were expressed as mean ± SD. Groups were compared by Mann–Whitney U-test for not normally distributed variables or matched signed-rank test. Correlations between continuous variables were calculated using Spearman's rank correlation coefficients. All tests were considered significant at the 0.05 level.

Values of PAPP-A, which were not normally distributed, were presented as medians and ranges and were compared among the groups with the Kruskal–Wallis test. In case of significant differences between the groups, pair wise group comparison was performed using Wilcoxon rank-sum testing. Receiver operator characteristic (ROC) curves and the size of the area under ROC curve (AUC) were applied for the evaluation of the diagnostic accuracy of PAPP-A in patients with carotid artery stenosis. AUC > 0.9 indicates the highest diagnostic accuracy, 0.65–0.9 confident diagnostic utility and 0.5–0.65 low diagnostic accuracy. Areas under ROC curves for different tests were compared on the basis of their confidence intervals and the U-test. ROC analysis also allowed determination of specificity and sensitivity (HSS) of PAPP-A. The optimal decision rule (cut-off point) for prediction of neurological symptoms was determined by the Youden index (J = maximum {sensitivity + specificity − 1}) for each factor and their combinations. Adjustment for age, gender and degree of stenosis was performed using a linear regression model to estimate the coefficients of the linear equation for each factor of adjustment. All analyses were performed with SPSS 16.0 (SPSS Inc. Chicago, IL, USA).

Results

Clinical data

In this study, we evaluated 66 patients with high-degree carotid artery stenosis (degree of asymptomatic vs. symptomatic stenosis 87.8 ± 7.8% vs. 87.5 ± 10.2%). Out of this group, we obtained suitable plaque specimens of 18 symptomatic and 15 asymptomatic patients for histological and eight symptomatic and nine asymptomatic patients for immunohistochemical analysis. No differences were found between clinical variables, risk factor profiles and pharmacological treatment among the study groups (Table 2).

Serum assessment of PAPP-A

To determine whether the abundant expression of PAPP-A in unstable plaques might correspond with the elevated circulating levels of this biomarker, we measured PAPP-A levels in patients with high-degree asymptomatic and symptomatic carotid artery stenosis.

Mean PAPP-A serum levels in patients with clinically asymptomatic CS ($n = 29$) were 0.11 μg ml − (SD ± 0.05 μg ml^{-1}). Patients with symptomatic stenosis ($n = 37$) showed significantly lower PAPP-A serum values of 0.07 μg ml^{-1} (SD ± 0.09 μg ml^{-1}, $p = 0.025$). Following adjustment for age, gender and degree of stenosis, the differences between the groups remained statistically significant ($p = 0.050$). The coefficient of the linear regression model changed only minimally from −0.405 to −0.391. All three factors used for adjustment contributed equally to the result. Analysing plaque stability and PAPP-A expression patients with unstable and ruptured plaques ($n = 24$) showed significantly increased serum concentrations of PAPP-A compared with patients with stable plaques ($n = 20$, 0.112 ± 0.06 μg ml^{-1} vs. 0.074 ± 0.04 μg ml^{-1}, $p = 0.047$) (Fig. 1).

Subgroup analysis of serological values of PAPP-A still demonstrates that serological PAPP-A values in symptomatic patients were significantly higher in unstable carotid lesions: 0.54 (0.34–1.30) for unstable versus 0.39 (0.24–0.91) for stable lesions ($p = 0.035$). No differences were, however, observed in the subgroup analysis of asymptomatic patients: 1.16 (0.49–1.89) versus 1.09 (0.45–1.85) ($p = 0.791$).

Immunohistochemical localisation of PAPP-A

Immunohistochemistry with CD68 and PAPP-A antibody showed positive results in plaques of both asymptomatic

Table 2 Patient characteristics: Hypertension includes any treated or untreated pathological blood pressure, Diabetes mellitus includes any treated IDDM or NIDDM, Hypercholesterolemia is defined as >240 mg/ml, Renal disease is defined as a glomerular filtration rate of <70 ml/min, Coronary heart disease is defined according to the Canadian Class Classification >CCS II.

	Asymptomatic	Symptomatic	Total	*p*-Value
Patients	29 (43.9)	37 (56.1)	66	0.676[d]
Male[b]	21 (72.4)	25 (67.6)	46	
Female[b]	8 (27.6)	12 (32.4)	20	
Age (years)[a]	67.9 ± 8.2	68.1 ± 8.6	67.9 ± 8.4	0.816[d]
Risk factors[a]	2.4 ± 1.1	2.4 ± 1.0	2.4 ± 1.1	0.842[d]
Hypertension [b]	25 (86.2)	32 (86.5)	57 (86.4)	0.751[d]
Diabetes mellitus [b]	6 (20.7)	7 (18.9)	13 (19.7)	0.903[d]
Hypercholesterolemia[b]	23 (79.3)	28 (75.7)	51 (77.3)	0.883[d]
Tobacco use[b]	11 (37.9)	20 (54.1)	31 (47.0)	0.162[d]
Renal disease[b]	4 (13.8)	3 (8.1)	7 (10.6)	0.499[d]
CHD[b]	10 (34.5)	10 (27.3)	20 (30.3)	0.570[d]
Medication				
Thrombocyte aggregation inhibitors[b]	28 (96.6)	36 (97.3)	64 (96.9)	0.326[d]
Beta-Blockers[b]	19 (65.5)	23 (62.2)	42 (63.6)	0.893[d]
ACE-Inhibitors[b]	16 (55.2)	16 (43.2)	32 (48.5)	0.398[d]
Statins[b]	16 (55.2)	20 (54.1)	36 (54.6)	0.976[d]
Vasodilatators[b]	5 (17.2)	0	5 (7.6)	0.023[d]
Degree of Stenosis (%)[a]	87.8 ± 7.8	87.5 ± 10.2	87.6 ± 9.1	0.751[c]
Peak systolic velocity (cm/s)[a]	377.7 ± 151.6	341.5 ± 163.9	358.3 ± 158.0	0.536[c]

[a] Data given as mean ± SD.
[b] Data are numbers of patients unless otherwise indicated, number in parentheses are percentages.
[c] *P* Value obtained with Mann–Whitney U Test.
[d] *P*-Value obtained with Chi-Square-Test.

and symptomatic patients. Enhanced expression of PAPP-A was associated with macrophage foam cells (CD68 positive), especially in cap and shoulder region of the plaques (Fig. 2). Focussing on the expression of PAPP-A in atheromatous plaques and CD68-positive cells, a significant correlation was observed ($n = 17$, correlation coefficient $r = 0.291$, $p < 0.001$). Mean occurrence of foam cells in stable plaques was 1.4% of the whole plaque area and 2.4% in unstable plaques.

In asymptomatic patients macrophage-associated PAPP-A expression was detected in 57.1% of stable plaques and in 95.0% of unstable plaques. Focussing on the symptomatic group, 28.5% of the stable plaques showed expression of PAPP-A; in unstable plaques it was detected in 68.9% (Fig. 3).

A positive correlation between PAPP-A expression in histological specimens and PAPP-A serum concentration was observed ($n = 17$, correlation coefficient $r = 0.618$,

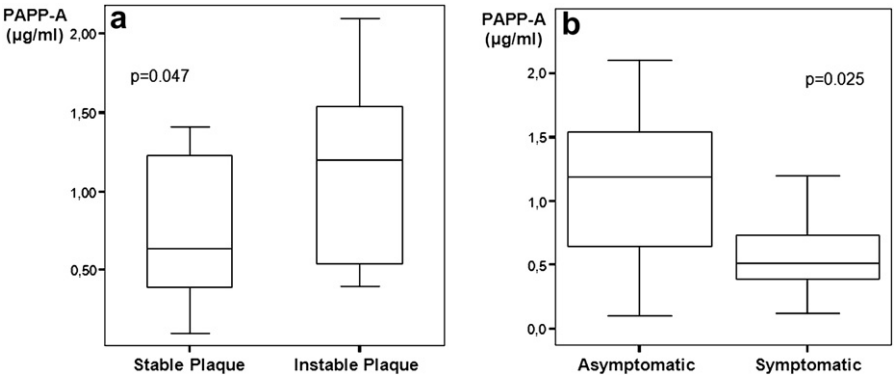

Figure 1 Serological concentration of PAPP-A in patients in correlation to plaque stability (a, $n = 33$) as well as to clinical neurological symptomatology (b, $n = 66$).

$p < 0.008$) (Fig. 4). Furthermore, PAPP-A expression in plaques correlated significantly with the cap thickness, leading to reduction of the fibrous cap and increase of PAPP-A expression (correlation coefficient $r = -0.639$, $p < 0.001$) (Fig. 5).

ROC analysis was performed to examine the performance of PAPP-A expression as well as the symptomatology by plotting the fraction of true positives rate against false-positive rate (Fig. 6). Cut-off values for asymptomatic and symptomatic stenosis as well as plaque stability were determined by using the Youden index (J = maximum {sensitivity + specificity − 1}) based on ROC curves (Table 3). The cut-off values of PAPP-A were as follows: patients with serum levels higher than 0.395 $\mu g\,ml^{-1}$ were classified as symptomatic (positive predictive value) (Fig. 6(a)), patients with PAPP-A lower than 0.555 $\mu g\,ml^{-1}$ were considered as asymptomatic (Fig. 6(b)).

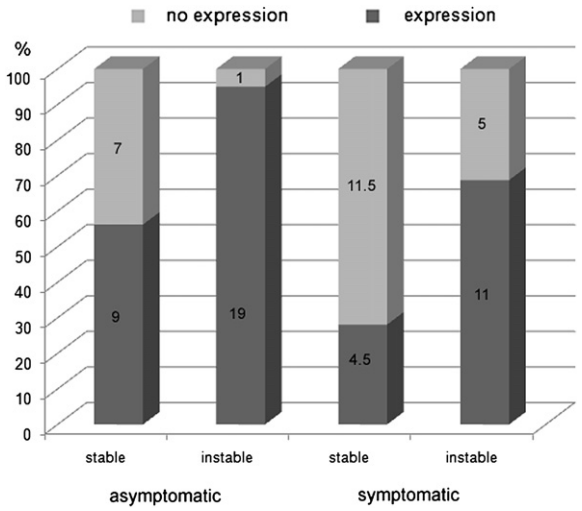

Figure 3 Overview of expression of PAPP-A in carotid artery plaques. Therefore plaques of 17 patients were evaluated. In each plaque four consecutive cross sections within the area of highest degree of lumen stenosis were analysed histologically.

Discussion

Disruption of carotid atherosclerotic plaque and subsequent embolisation of debris is a common pathogenic mechanism for cerebral ischaemia. Plaque vulnerability is associated with an increased number of inflammatory cells at the atheromatous site.[8] Activation of macrophages leads to the secretion of various metalloproteinases, which cause a weakening of plaque tissue and eventually leads to plaque rupture.[9] PAPP-A is a high-molecular-weight zinc-binding matrix metalloproteinase and was originally identified in the plasma of pregnant women.[10–12] Vascular endothelial and smooth muscle cells are responsible for production and secretion of PAPP-A within atherosclerotic plaques.[3] PAPP-A is a local regulator of insulin-like growth factor-1 (IGF-1) activity and may thus promote the proatherogenic effects of IGF-1. Up-regulation of PAPP-A in unstable plaques suggests that the involvement of the PAPP-A system may be clinically relevant.[13–15] Despite the results of Dominguez[16] demonstrating that circulating PAPP-A levels does not sufficiently detect acute myocardial infarction (AMI) caused by plaque disruption, our results demonstrate a significant correlation of PAPP-A with the instability of carotid plaques.[16]

Metalloproteinases have already been associated with macrophage-rich shoulder regions of atherosclerotic lesions and implicated in plaque rupture.[17,18] In our study, we confirmed that PAPP-A is expressed by activated macrophages especially in fibrous caps and that expression of PAPP-A was associated with macrophages. Although the correlation was weak, we found a similar localisation in almost all specimens on immunohistological staining (see also Fig. 2). Therefore, the relatively weak correlation in our study might be due to the limitation of our analysing method.

Bayes-Genis found that PAPP-A was expressed in both eroded and ruptured plaques but was only minimally expressed in stable plaques of patients with cardiac disease.[3] Similarly, Elseber observed significantly higher serum PAPP-A levels in patients with unstable angina or acute myocardial infarction than in control subjects.[19] Based on these results, it was suggested that increased plasma levels of PAPP-A reflect the instability of

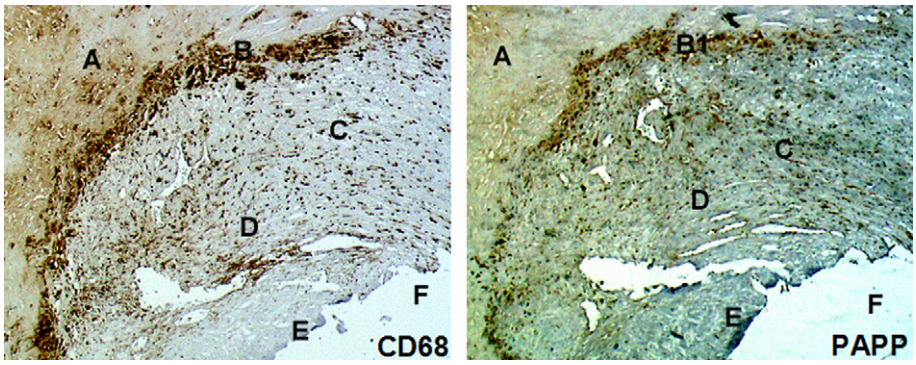

Figure 2 Immunostaining of carotid artery plaque with CD68 and PAPP-A to detect correlation of macrophage foam-cells and expresison of PAPP-A. Macrophage foam-cells (CD-68 positive) were found around the plaque shoulder and in the fibrous cap. (A) necrotic core, (B) macrophages, foam cells (immunostaining for CD68), (B1) immunostainig for PAPP-A positive macrophages, (C) macrophages, (D) fibrous area (collagen, proteoglycans), (E) endothelium, (F) vessel lumen.

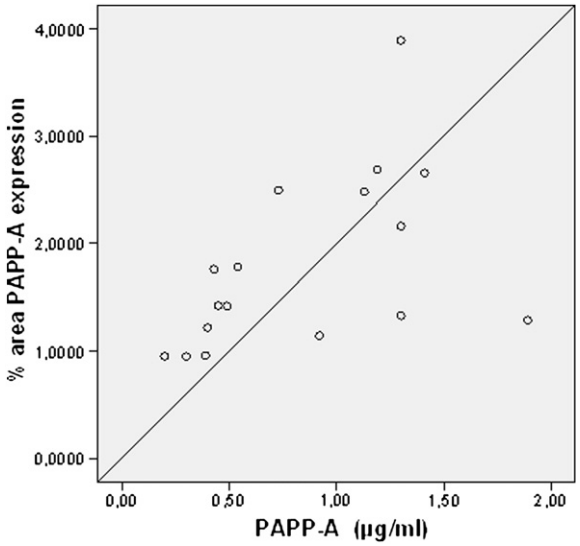

Figure 4 Graph showing correlation between serum values of PAPP-A (μg/ml) versus expression of PAPP-A in histological slices (correlation coefficient $r = 0.618$, $p < 0.008$). Therefore we measured areas of dense expression of PAPP-A-positive cells in relation to total cross section area. Data are calculated as areas of PAPP-expression − plaque area − ratio (% of Plaque area in mm^2).

atherosclerotic plaques and that PAPP-A might be a specific marker of acute coronary syndromes.[20] However, Cosin-Sales indicated that even in patients with stable coronary heart disease, PAPP-A levels are associated with morphological plaque complexity and predict recurrence of symptoms in patients with ACS.[4] Therefore, we compared serum PAPP-A levels in patients with neurologically asymptomatic and symptomatic CS with histopathological findings to evaluate the prognostic significance of PAPP-A with regard to destabilisation of atherosclerotic plaques. In accordance with Sangiorgi, we demonstrated that unstable plaques are present in both asymptomatic and symptomatic patients.

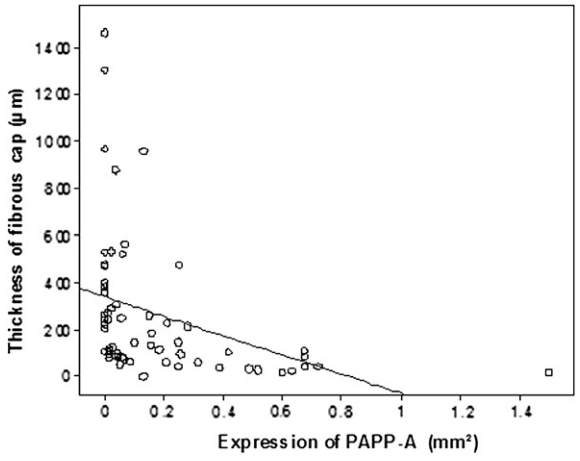

Figure 5 Correlation of thickness of fibrous cap and expression of PAPP-A in macrophages was evaluated in 68 cross sections of 17 patients. p-value < 0.001; $r = -0.639$ (non-parametric measurement of correlation by Spearman).

Furthermore plaque stability correlated significantly with expression of PAPP-A within the carotid lesions in our study.[21] Moreover, we could demonstrate a correlation between the serological concentration of PAPP-A and its expression in plaques as well as a correlation between expression of PAPP-A in plaques and thickness of fibrous caps.

Elevated oxidative stress is believed to play an important role in plaque destabilisation. Previous studies demonstrated a high proteolytic activity of PAPP-A when it is not bound in a covalent complex with the proform of eosinophil major basic protein (proMBP).[11,22] This is a reason for the detection of PAPP-A in the blood secreted by atherosclerotic plaques. High uncomplexed amounts of circulating PAPP-A could be a marker of oxidative stress. Stulc and Miedema described that serum PAPP-A levels were significantly higher in patients with severe hypercholesterolemia than in healthy normolipidaemic control subjects, despite the absence of clinically manifest atherosclerosis.[20,23] This suggests that an increase in PAPP-A may reflect earlier stages of atherosclerotic lesions, even in the absence of clinical signs of atherosclerosis. We demonstrated a correlation between a decrease of fibrous cap thickness and expression of PAPP-A. Particularly in asymptomatic patients, we detected a group of patients with rupture-prone plaques and high levels of PAPP-A. In our opinion, these results demonstrate highly active plaque formations in a clinically still silent situation. However, the interpretation of increased PAPP-A levels is difficult. The values reported to date for patients with acute coronary syndrome differ substantially and a threshold value for unstable plaques or preclinical atherosclerosis still does not exist and needs careful evaluation.

In contrary to recent studies, we found higher circulating levels of PAPP-A in clinically asymptomatic CS. We hypothesise that we measured free and membrane-bound PAPP-A with high proteolytic activity, while symptomatic CA has internalised PAPP-A with little or no protease activity.[24] Qin reported that only the free form of PAPP-A is relevant in such patients.[25] Harrington already found that loss of PAPP-A has a predominant effect on lesion progression rather than lesion initiation.[26] In our opinion, a high circulating level of PAPP-A is a sign of developing 'juvenile' unstable plaques. Given its proteolytic potential and the associations between concentrations and atherosclerotic plaques, PAPP-A may contribute to the degradation of a plaque's extracellular matrix.[27]

Previous studies with PAPP-A in cardiovascular disease showed a sensitivity of 89% and specificity of 79%.[28] In our study, we achieved an adequate sensitivity and specificity with a promising positive predictive value to determine plaque instability accurately. We believe that disruption of carotid plaques releases PAPP-A to the circulation in the early phase before severe clinical neurological symptoms appear. In our opinion, it makes PAPP-A an interesting biomarker for the detection of rupture-prone plaques and an impending neurological event, especially in patients with asymptomatic carotid artery stenosis. However, more prospective studies in carotid artery patients are required to evaluate the exact mechanism by which PAPP-A promotes atherogenesis as well as to validate its utility in diagnosis and therapeutic guidance.

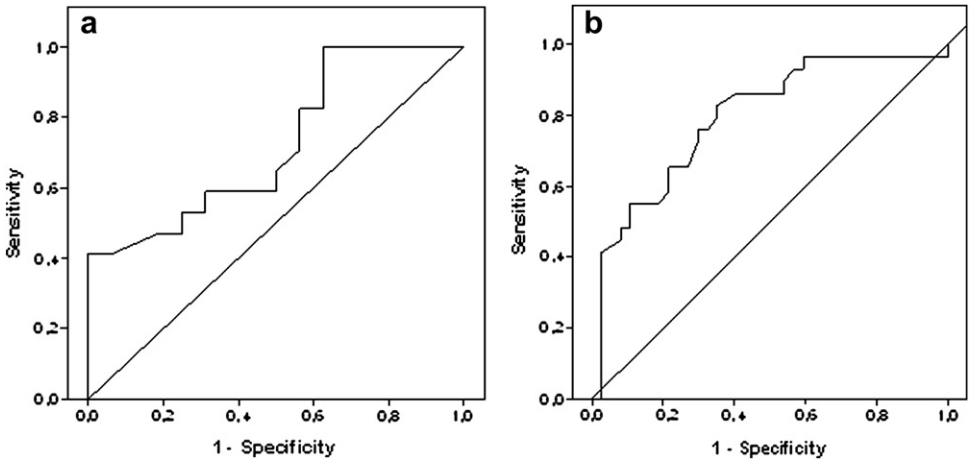

Figure 6 a: ROC curves for comparison of the performance of the expression of PAPP-A in serum vs. instability of the carotid plaque; b: expression of PAPP-A in serum vs. clinical neurological status (asymptomatic patient) of the patient. The curve above the diagonal shows the true-positive against the false-negative rate for determination of possible cut-off values of a prediction algorithm as a trade-off between sensitivity and specificity. The greater the AUC (area under curve), the more accurate is the model.

Study Limitations

Despite careful and detailed data analysis, our study has some limitations. First, we cannot exclude the possibility that the PAPP-A level in blood of the study patients could originate from other unstable plaques than carotid. It is, however, known that most cardiovascular events are caused by thrombotic occlusion of a single plaque and not multiple plaque rupture.[29] Therefore, we assumed that the increased PAPP-A level was caused by the unstable carotid lesion. However, we cannot completely exclude the possibility that, in some patients, the increase of PAPP-A could also have other reasons. Second, in contrast to the study of Sangiorgi, our data demonstrated an overall increased PAPP-A level in asymptomatic patients. The reason for this discrepancy could be that we only measured free PAPP-A in blood. It is, however, known that upon activation and inflammatory reaction, two PAPP-A forms, complexed and uncomplexed with proMBP, can be found and this PAPP-A is not recognised by the assay we have used in our study. Thus, the lower level of PAPP-A in the symptomatic patients may be only due to the less free PAPP-A.

Table 3 Combined sensitivity, specificity and positive predictive value (PPV) for optimal cut-off points[a] (plaque stability in histological specimen and neurological symptoms). PAPP-A was measured in serum (μg/ml).

	Cut-off point	Sensitivity (%)	Specificity (%)	PPV
Plaque stability	0.395	100	62.5	68.8
Neurological symptomatology	0.555	82.8	35.3	73.7

[a] The optimal decision rule (cut-off point) for prediction of neurological symptoms was determined by using Youden index (J = maximum {sensitivity + specificity − 1}) for each factor.

Conclusion

The present study provides evidence that circulating levels of PAPP-A are associated with an enhanced inflammatory state and a shift from stable to unstable carotid artery disease. Plaque rupture is a common cause of stroke and our results suggest that circulating PAPP-A levels might be an early marker of the processes leading to plaque instability and rupture. Nevertheless, using concentrations of circulating PAPP-A for the diagnosis of rupture-prone carotid lesions still needs careful consideration. Further tests with larger studies are needed to prove the relevance of PAPP-A as a prognostic marker for the presence of vulnerable plaques and its role in stroke prevention.

Conflict of Interest

None declared.

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