Poor Response to Activated Protein C as a Prominent Risk Predictor of Advanced Atherosclerosis and Arterial Disease

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Background—The potential role of activated protein C (APC) resistance in arterial thrombosis and disease is a matter of ongoing controversy.

Methods and Results—In the present population-based survey, a random sample of 826 men and women underwent high-resolution duplex ultrasound scanning of the carotid and femoral arteries. Response to APC was expressed in APC ratios. Subjects were tested for the factor V Leiden mutation. The risk of carotid stenosis increased gradually with decreasing response to APC (adjusted OR [95% CI] for a 1-U decrease of response to APC, 1.6 [1.2 to 2.2]), as did the risk of femoral artery stenosis (1.7 [1.3 to 2.3]) and prevalent cardiovascular disease (1.4 [1.1 to 2.0]). The association between low APC ratio and atherosclerotic vascular disease applied equally to subjects with the factor V Leiden mutation and those without. Our study identified various nongenetic determinants of poor response to APC in the general population, including behavioral, hormonal, and environmental factors.

Conclusions—The present study revealed an independent and gradual association between low response to APC and both advanced atherosclerosis (stenosis) and arterial disease. Resistance to APC due to factor V Leiden mutation was only one facet of this relationship. (Circulation. 1999;99:614-619.)

Key Words: proteins ■ atherosclerosis ■ arteries ■ cardiovascular diseases ■ thrombosis ■ ultrasonics

During normal hemostasis, activated protein C (APC) counteracts thrombin amplification and clot propagation by an enzymatic degradation of factors Va and VIIIa.1 In 1993, Dahlbäck and coworkers2 were the first to describe resistance to APC in patients with venous thromboembolic events. This condition is frequently3–5 but not exclusively6 caused by a point mutation in the cleavage region of factor V. Meanwhile, a broad consensus has been reached on the prominent role of APC resistance in idiopathic and familial venous thrombosis.7,8

As a key outstanding question, the transferability of this finding to arterial thrombosis remains to be elucidated. Atheroma-associated thrombus formation and organization are widely accepted as one main pathomechanism in the development of vessel stenosis and occlusion.9 The present study was designed to analyze the strength and type of association between response to APC expressed in APC ratios and both manifest arterial disease and advanced (stenotic) atherosclerosis in the carotid, femoral, and lower limb arteries. It addresses the role of factor V mutation as part of this association and attempts to further identify the main determinants of poor APC response in the general healthy population.

Study Population
APC ratios were measured as part of the first follow-up examination of the Bruneck Study. Special features of the survey area and study protocol have been detailed previously.10 In brief, at the 1990 baseline, the study population was recruited as an age- and sex-stratified random sample of all inhabitants of Bruneck (Bolzano province, Italy) 40 to 79 years old (125 women and 125 men in their 5th to 8th decades). A total of 93.6% participated, with data assessment completed in 919 subjects. Between 1990 and 1995, a subgroup of 63 individuals died or moved away. In the remaining population, follow-up was 96.5% complete (n=826). All participants gave informed consent before entering the study.

Clinical History and Examination
The systolic blood pressure was taken in a sitting position after at least 10 minutes of rest (mean of 3 independent measurements).10 The ratio of ankle to brachial systolic blood pressure was assessed separately in both lower limbs.11 The average number of cigarettes smoked per day was noted for each smoker and ex-smoker. Regular alcohol consumption was quantified in terms of grams per day.

Major Clinical Events
In an effort to identify all cardiovascular events that had occurred in the Bruneck Study population, we performed an extensive screening...
using the following sources of information: Rose questionnaire,12 detailed self-reported medical and medication history, cardiological and neurological examination, resting ECG, medical records provided by general practitioners, and medical records from Bruneck Hospital. The situation in this geographically remote mountainous region is unique in that the whole area is served by Bruneck hospital only, and the only facilities for exercise ECG and echocardiography and the only ambulatory service for cardiology and neurology are located at the hospital. All medical records were collected from Bruneck Hospital databases and thoroughly reviewed for diseases of interest. Myocardial infarction was deemed confirmed when World Health Organization criteria for definite disease status13 were met, including compatible symptoms and either elevated cardiac enzymes or ECG changes. Coronary heart disease was ascertained by means of standard diagnostic criteria, including typical resting (Minnesota codes 1.1 to 1.2, 4.1 to 4.2, 5.1 to 5.2, or 7.1) or exercise ECG and/or pathological coronary angiography and/or echocardiography. Stroke and transient ischemic attack were classified according to the criteria of the National Survey of Stroke.14 The diagnosis of peripheral artery disease required a positive response to the Rose questionnaire, with the vascular nature of complaints confirmed by standard diagnostic procedures and/or a documented history of previous aortofemoral or femoropopliteal bypass surgery (n=10).

Laboratory Parameters

Blood samples were collected after subjects had fasted and abstained from smoking for at least 12 hours.10 In 5 subjects with recent stroke or myocardial infarction, samples were drawn at an interval of 3 months. For the coagulation assay, citrated plasma was obtained by centrifugation at 2500g for 10 minutes (15°C) immediately after sampling. Special care was exercised to prevent contamination of platelets from the platelet layer. The plasma was kept frozen at −70°C for a period of <3 months, and the response of plasma activated partial thromboplastin time (aPTT) to APC was expressed as the ratio of clot time of APC/CaCl2 to clot time of CaCl2 (Coatest APC resistance, Chromogenex).4,15 In an effort to assess the reproducibility of this method, we performed triple measurements in subjects with APC ratios of ~2.0 and 3.5 (n=30 each). Interassay coefficients of variation were low, 5.2% and 3.2%. Plasma from 1 patient on heparin therapy was pretreated with heparinase, a heparinase that neutralizes heparin effects on PTT.4,16 Commercial factor V–depleted serum (Boehringer-Mannheim) was used for standardized dilution of plasma samples (1:5) from patients taking warfarin (n=10) to ensure reliable APC ratio estimates in this subgroup. Plasma from 50 apparently healthy subjects without a family history of venous thrombosis, regular medication, or evidence of recent infections was pooled to serve as a reference plasma (mean APC ratio/APC ratio of pool plasma.3,4 Levels of β-thromboglobulin were assessed in a random subsample of the Bruneck Study population11 (n=80, plasma frozen at −70°C for 2.5 years) and in 80 fresh plasma samples collected in 1998 (Asserachrom, Boehringer-Mannheim). Apolipoproteins B and A-I were measured by a nephelometric fixed-time method (coefficient of variation, 5.7% and 2.4%). Proteins C and S were assessed with commercial assays (Protein S Asserachrom, Boehringer-Mannheim; normal range, 70% to 140%; protein C chromogenic assay, 70% to 130%). Diagnosis of lupus anticoagulant was achieved by measurement of lupus anticoagulant–sensitive aPTT (Baxter/Laevosan; cutoff, >1.3) and the diluted Russel viper venom time test (American Diagnostic Inc; cutoff, >1.8). An ELISA was used to measure anti-cardiolipin (Diamedix; cutoff for IgG, >10 U/L and IgM, >7.5 U/L) and anti–β2-glycoprotein antibodies (Inova Diagnostics Inc; cutoff, >10 U/L). Genomic DNA was prepared by the DNA Zol method.18 Samples were investigated with 2 polymerase chain reaction (PCR) amplifications, one amplifying the wild-type and the other amplifying the factor V point mutation. Each PCR mix included a primer pair that amplified a fragment of the human growth hormone gene (internal positive amplification control13–18).

### Table 1. Multivariate Association of APC Ratio With Environmental Factors, Laboratory Parameters, and Vascular Risk Attributes in the General Population (n=826) Assessed by Multiple Linear Regression Analysis With Forward Stepwise Selection

<table>
<thead>
<tr>
<th>Regression Coefficient (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.009 (−0.013 to −0.005)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.502 (0.338 to 0.667)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>0.317 (0.154 to 0.480)</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>−0.405 (−0.512 to −0.298)</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>−0.090 (−0.138 to −0.041)</td>
</tr>
<tr>
<td>Partial thromboplastin time, s</td>
<td>0.034 (0.013 to 0.055)</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>0.002 (0.001 to 0.003)</td>
</tr>
</tbody>
</table>

*Regression coefficients for all variables were expressed per unit of measurement. When normalized APC ratios were applied as the dependent variable, the regression coefficients had to be multiplied by the factor 0.32.

### Evaluation of Vascular Status

Sonographic assessment was performed with a duplex ultrasound system equipped with a 10-MHz imaging probe and a 5-MHz Doppler. The scanning protocol included imaging of the right and left common (proximal and distal segments), internal (bulbous and distal segments), and external carotid arteries15 and of the femoral arteries 40 mm proximal and 10 mm distal to the bifurcation into the superficial and deep branches. Atherosclerotic lesions were defined as echogenic lesions encroaching into the lumen. Doppler criteria or, when no hemodynamic disturbances were detectable, a diameter reduction of >40% in the B-mode images was applied to define stenosis. The cutoff of 40% appeared to be a biological threshold: in brief, nonstenotic atherosclerosis showed a slow, continuous, and diffuse type of lesion extension compensated by vessel dilation. This process emerged as a domain of traditional risk factors, such as hyperlipidemia. In contrast, the development of stenosis >40% was characterized by occasional prominent plaque growth, long stable periods, focal manifestation, and a procoagulant risk profile indicative of underlying plaque thrombosis. Failure in vascular remodeling and marked increases in plaque size acted synergistically in producing significant lumen compromise. Actually, some 95% of stenosis >40% originated from this type of atherogenesis.

### Statistical Analysis

The assumption of normality for the APC ratio distribution, implicit in basing analysis on parametric statistics, was checked and confirmed by detrended normal plots and the Lilliefors test (P>0.20).19 The relation between APC ratios and other variables was assessed by linear regression analysis. A multivariate regression model was built with a forward stepwise selection procedure (probability values for entry and removal of variables, 0.15 and 0.2020,21). To evaluate the association between response to APC and stenotic atherosclerosis, logistic regression models were fitted with the test procedure on the basis of maximum likelihood estimates.22 In an attempt to obtain the most suitable parametric scale in the logit, 5 equally spaced categories of APC ratios were modeled with indicator variables in separate analyses. Trends were estimated by visual inspection of plots of the logit against the midpoints of APC categories and by application of orthogonal polynomials.21 For ease of presentation, the multivariate analyses for all outcome variables were adjusted for the same set of covariates by forced entry of these variables, and ORs derived from these models are referred to as adjusted ORs in the text. The list of covariates includes age and sex, the main determinants of APC ratio (Table 1); cardiovascular risk factors; and drug therapy (see Table footnote). Analogous logistic regression models were built by use of a forward stepwise selection procedure. The 2 approaches yielded virtually identical results.
**Results**

In our population, responses to APC expressed in APC ratios ranged from 1.4 to 5.1 (n-APC ratio, 0.4 to 1.9). Mean APC activity was significantly higher in men than in women (Figure). The APC ratio decreased with increasing age by 0.07 per decade (95% CI, 0.4 to 1.0) (n-APC, 0.02 [95% CI, 0.01 to 0.03]). Further significant associations were found for acute-phase reactants (C-reactive protein, α1-antitrypsin, co-
TABLE 2. Risk of Vessel Stenosis and Cardiovascular Disease According to Level of Response to APC in the Bruneck Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Response to APC*</th>
<th>APC Ratio ‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥3.50 (n=207)</td>
<td>3.49–3.00 (n=264)</td>
<td>2.99–2.50 (n=233)</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n (%)</td>
<td>31 (15.0)</td>
<td>46 (17.4)</td>
<td>51 (21.9)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Adjusted for age and sex</td>
<td>1.0</td>
<td>1.3 (0.8–2.2)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment§</td>
<td>1.0</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment¶</td>
<td>1.0</td>
<td>1.4 (0.8–2.4)</td>
</tr>
<tr>
<td>Femoral artery stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n (%)</td>
<td>29 (14.0)</td>
<td>47 (17.8)</td>
<td>54 (23.2)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Adjusted for age and sex</td>
<td>1.0</td>
<td>1.3 (0.8–2.1)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment§</td>
<td>1.0</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment¶</td>
<td>1.0</td>
<td>1.3 (0.8–2.3)</td>
</tr>
<tr>
<td>CVD‡</td>
<td>Cases, n (%)</td>
<td>18 (8.7)</td>
<td>18 (6.8)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Adjusted for age and sex</td>
<td>1.0</td>
<td>1.4 (0.8–2.5)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment§</td>
<td>1.0</td>
<td>1.3 (0.8–2.2)</td>
</tr>
<tr>
<td></td>
<td>Multivariate adjustment¶</td>
<td>1.0</td>
<td>1.5 (0.8–2.6)</td>
</tr>
</tbody>
</table>

*Response to APC is expressed as the ratio of activated thromboplastin time with the addition of APC to activated thromboplastin time without the addition of APC. Normalized APC ratios are calculated by dividing the native ratios by 3.16.
†P value for the association between APC categories (dR2=4) and atherosclerotic vascular disease.
‡ORs and P values were derived from logistic regression analysis that treats APC ratio as a continuous variable. ORs apply to a 1-U decrease in the APC ratio.
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$CVD subsumes nonfatal ischemic stroke and transient ischemic attack, coronary disease, and peripheral artery disease.

eruloplasmin, fibrinogen), alcohol consumption, PTT, anti-thrombin III, and cholesterol levels. A multivariate prediction model of APC activity is given in Table 1. All independent determinants in concert accounted for 25% of the variability of APC ratios (R2=0.23). Levels of β-thromboglobulin, a platelet activation marker, showed a rather low variability in 2 population samples, each containing 80 subjects (frozen plasma samples: mean [interquartile ratio], 5878 IU/mL [4450 to 7604 IU/mL]; fresh plasma samples: 5948 IU/mL [4680 to 7480 IU/mL], and did not correlate with APC ratios (r=0.023 and 0.013, respectively).

The allele frequency of the factor V mutation in our population was 1.5%. Functional tests for response to APC are frequently used to screen for the mutation. At the recommended cutoff for our coagulation assay (<2.0U), the sensitivity for detection of the Leiden mutation was 75% and the positive predictive value 42%. In >50% of subjects with an APC ratio<2.0 (prevalence, 5.4% [95% CI, 3.9% to 6.9%]), DNA analysis remained negative. In a minority of these individuals, APC resistance may be explained by protein C deficiency (n=1), presence of lupus anticoagulant (n=1), or infectious diseases (n=3). None had a protein S level <20%. Anti-cardiolipin or anti-β2-glycoprotein antibodies were found in 5 subjects with factor V–independent APC resistance and 4 subjects with the Leiden mutation (coincidence, 20% each).

Men and women with nonstenotic carotid or femoral atherosclerosis and those without atherosclerotic lesions did not differ in their mean responses to APC (APC ratio, 3.20 each). For ease of presentation, these subjects were grouped together and compared with patients with stenotic atherosclerosis, which is the group with a putative pathogenetic relevance of arterial (plaque) thrombosis. When this was done, the analysis revealed a strong and independent association between APC ratio and the risk of stenosis >40% in carotid or femoral arteries, regardless of whether APC ratio was modeled as a categorical or continuous variable (Table 2). The scale fitting procedure described in the Methods section documented an excellent fit of a linear (dose-response) relation across the entire range of APC ratios (P<0.001 for the linear component of orthogonal polynomials). The association remained independently significant after control for potential confounders and aspirin medication (Table 2). Separate models that were additionally adjusted for use of β-blockers (n=50) and ACE inhibitors (n=76) yielded virtually identical results (adjusted ORs [95% CIs], 1.8 [1.3 to 2.5] and 1.7 [1.2 to 2.4] for carotid and femoral artery stenosis).

Temporary APC resistance may occur in the course of infectious diseases and introduce a bias in the association between APC ratio and arterial disease.
the analysis after excluding subjects with laboratory evidence of ongoing acute-phase reaction (C-reactive protein $>$ 2.5 mg/L; n = 18). This procedure tended to strengthen the association rather than to dilute it (Table 2).

The association between poor response to APC and advanced atherosclerosis emerged as independent of the presence of factor V mutation: in particular, among subjects with APC ratios $<2.0$, excess risk of carotid stenosis applied equally to those with the Leiden mutation (adjusted OR [95% CI], 3.6 [1.1 to 11.7]; reference group with APC ratio $\geq 3.5$) and those without (3.9 [1.4 to 10.9]). Likewise, individuals with the factor V mutation and with factor V–independent APC resistance faced a similar risk of femoral artery stenosis (2.9 [1.1 to 7.8]; versus 3.4 [1.4 to 8.4]).

In subjects on aspirin therapy that was initiated for reasons other than known carotid vessel pathology (n = 80), the predictive significance of low APC ratio for advanced atherosclerosis was clearly less pronounced than in untreated individuals (adjusted OR [95% CI], 0.9 [0.4 to 2.1] versus 2.5 [1.7 to 3.7]; $P = 0.033$ for effect modification).

An ankle/brachial pressure index $\leq 0.8$ is another validated indicator of hemodynamically relevant stenosis of the femoral and lower limb arteries.11 When this outcome variable was substituted for the ultrasound end points, the adjusted OR (95% CI) for a 1-U decrease in the APC ratio was 1.8 (1.1 to 3.1).

Finally, response to APC emerged as a significant risk predictor of prevalent nonfatal cardiovascular disease (CVD) (Table 2). Subanalyses fitted separately for the different types of arterial disease yielded results as follows: transient ischemic attack and stroke (n = 37): 1.7 (1.0 to 2.8). These results should be interpreted in the light of the low number of events in each disease category. In subjects who suffered fatal CVD between 1995 and 1998 (n = 15), APC ratios were significantly lower (mean, 2.67) than in those who died of causes other than CVD (n = 33) (mean, 3.15) or those still alive without manifest vascular illness (mean, 3.16; $P < 0.05$ each). Likewise, factor V mutation was overrepresented (7% versus 0% and 2%).

**Discussion**

**Response to APC and Advanced Atherosclerosis**

As anticipated, plaque thrombosis is a main pathomechanism in the development of vessel stenosis and occurrence of arterial disease, and the protein C anticoagulant system ranks among the most potent control mechanisms of excess thrombosis in vivo.1 To date, however, the concept that poor anticoagulant response to APC is involved in advanced stages of atherogenesis has received limited attention in epidemiological research. The present survey is the first to demonstrate a (linear) dose-response relation between decreasing APC ratio and increasing risk of advanced atherosclerosis (stenosis) in the carotid, femoral, and lower limb arteries. The predictive significance of poor response to APC did not extend to nonstenotic atherosclerosis, corresponding to the fact that this type of early vessel pathology actually does not rely on plaque thrombosis.9

Poor response to APC due to factor V mutation, although per se a strong risk condition of advanced atherosclerosis, was only one (rare) facet of the overall relation, which emphasizes the need to characterize further genetic and environmental determinants of APC response in the general population. To date, such data are rather sparse.23 In our population sample, regular alcohol consumption was associated with increased APC ratios. Premenopausal women exhibited lower APC ratios than did women after menopause or men. This finding, taken together with the decrease of APC ratios during pregnancy and estrogen supplementation, points to effects of hormone status and hormonal shifts in the protein C system.24 Given that some regulatory components of the protein C pathway ($\alpha_{1}$-antitrypsin, C4bBP) increase in response to infectious stimuli as part of the acute-phase reaction,18 emergence of an inadequate APC action (procoagulant state) confined to the period of acute disease was not unexpected. In accordance with recent population surveys, greater age and increased LDL cholesterol levels emerged as further empirical predictors of inefficient APC action.4,23 Finally, APC ratios did not correlate with $\beta$-thromboglobulin levels. Thus, variable platelet contamination and/or activation appears not to be a major source for the variability of APC ratios in our population.

Notably, fewer than 50% of APC-resistant subjects, who are considered potential carriers of factor V mutation, actually had this genetic disorder. In the remaining group, APC resistance was unknown in origin except for a few cases with protein C deficiency, lupus anticoagulant, or prominent protease inhibitors (C4bBP) for an impaired APC action (procoagulant state) confined to the period of acute disease was not unexpected. In accordance with recent population surveys, greater age and increased LDL cholesterol levels emerged as further empirical predictors of inefficient APC action.4,23 Finally, APC ratios did not correlate with $\beta$-thromboglobulin levels. Thus, variable platelet contamination and/or activation appears not to be a major source for the variability of APC ratios in our population.

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**Response to APC and CVD**

As expected, in view of the association with advanced atherosclerosis, poor response to APC emerged as a significant risk predictor of nonfatal CVD. Subjects with the Leiden mutation were at a particularly increased risk of arterial disease. Predictive significance was not confined to this genetic disorder but rather extended to poor response to APC of distinct origin. Preliminary data suggested analogous results for fatal CVD.

The number of previous reports advocating a risk factor status of an impaired protein C anticoagulant pathway for arterial disease is approximately in balance with the number of those that failed to observe any relation.29–31 Inconsistency in the results observed may be explained by the profound differences in the study design: (1) A majority of studies applying coagulation assays reported a significant relation, whereas results from DNA-based analyses were contradictory. Analyses focusing on the Leiden mutation may lack statistical power because subjects with poor response to APC due to other genetic and environmental factors who are at an equally high risk of atherosclerosis were included in the reference group. (2) Long-term aspirin treatment appeared to
level the predictive significance of low APC ratios for advanced atherosclerosis. Most previous studies did not control for this potential source of bias. One was designed as an intervention trial testing the efficacy of aspirin in the primary prevention of CVD.29 (3) Negative studies are in part hospital-based.30,31

Methodological Considerations

So far, no consensus has been reached on a standard laboratory method for measuring response to APC. The present study provides evidence against the use of DNA-based tests and clotting assays specific to factor V (Arg506Gln) mutation, given that the predictive significance of poor response to APC for arterial disease was not restricted to the Leiden mutation. Our coagulation assay was standardized in a multicenter trial15 and is widely used in clinical research.2,8,15,25 Although interlaboratory variability was found to be low,15 some residual variation may arise from differences in plasma preparation and laboratory equipment.4,15,23 Normalization of APC ratios to a reference plasma has been suggested to overcome this problem.3,4

In conclusion, the present epidemiological survey revealed an independent and gradual association between poor response to APC and the risk of arterial disease and suggests promotion of advanced atherosclerosis as a main underlying pathomechanism. Biological plausibility, a dose-response type of relation, and the excellent consistency of results for various vascular territories, along with distinct ultrasonographic, pressure index, and clinical end points, all favor significance beyond a purely mathematical relation. The APC ratio was associated with a variety of genetic, environmental, hormonal, and behavioral factors, some of which are potentially modifiable. From a preventive perspective, the absence of a relation between response to APC and advanced atherosclerosis in subjects under long-term aspirin therapy seems interesting, although the reliability of this finding is clearly limited by the observational study design.

References

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