Comparison of the Prevalence of APC-resistance in Vascular Patients and in a Normal Population Cohort in Western Germany

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Objective. To compare the prevalence of APC-resistance (APC-R) in patients with peripheral vascular disease and the general population.

Design. Prospective cohort examination.

Materials and methods. Three hundred and eleven patients (group A) suffering from arterial occlusive disease or an abdominal aortic aneurysm were prospectively screened for APC-R. There were 228 men and 83 women with a mean age of 65 years (20–88 years). Two hundred and sixty patients underwent an open surgical or interventional procedure. A total of 306 patients were followed clinically for an average of 8 months (1–31 months). Two hundred and seven healthy volunteers (group B) served as a control group.

Results. The prevalence of a functional APC-R was 11% (33/311) and 8% in groups A and B, respectively, (p = 0.272). APC-R did not occur more frequently among patients who were treated primarily for a bypass occlusion (3/21 vs 30/290) (p = 0.476). None of five patients who had a postinterventional graft or vessel occlusion (1.9%) had an APC-R. Sixteen patients (5%) experienced an arterial occlusion during follow-up of which two had APC-R.

Conclusions. Previously published increased prevalence rates of APC-R in patients with arterial disorders could not be confirmed in this study. A firm association between the presence of APC-R and previous bypass occlusion or postoperative failure of the vascular reconstruction could not be demonstrated.

Keywords: Arterial diseases; APC-resistance; Vascular surgery.

Introduction

According to Virchow’s triad changes of blood flow, a diseased vessel wall and alterations of the blood contents favour thrombosis. Deficiencies in physiological inhibitors of coagulation like antithrombin III, protein C and S thus, promote thrombus formation. Resistance to activated protein C (APC-R) is the commonest inherited coagulation disorder associated with deep vein thrombosis, however, the association with arterial thrombosis is less clear. A higher prevalence of APC-R could be shown among younger individuals having a stroke or myocardial infarction compared to the normal population. The impact of APC-R on postoperative failure of vascular reconstructions remains unclear.

Previously published data demonstrates demographic and geographic differences in APC-R prevalence in the normal population, which varies between 3 and 8%. In contrast to the Caucasian population, APC-R is rarely seen or even unknown in the native people in East Asia (Indonesia, Japan, China), Africa, Australia or South America. The aim of this study was to assess the relationship between APC-R and arterial disease in a population in Western Germany.

Materials and Methods

From January until December 2000, 311 consecutive patients (228 men, 83 women) with an average age of 65 years ranging from 20 to 88 years were electively treated in our department for either peripheral arterial occlusive disease (PAOD, n = 240) or abdominal aortic aneurysm (AAA, n = 71). The patients were prospectively screened for APC-R using a functional test.
determining the APC-ratio (Coatest® APC™ Resistance V, Chromogenix, Italy). The standard PTT time (PTT1) is compared to a second measurement in which APC is added leading to inactivation of factor Va and a prolongation of PTT (PTT2). The ratio of PTT2/PTT1 will, therefore, be lower than the reference range in the case of APC-R. If the functional test showed a pathological result (APC-ratio <2.1) Factor V-Leiden mutation was sort using PCR (LightCycler®, Roche Diagnostics, Germany).

After taking the medical history, the patients underwent a complete physical examination including a detailed vascular assessment and the ankle-brachial index (ABI) measurement. A detailed description of the interventional procedures is given in Table 1. The patients were screened for the presence of risk factors including immobilisation, trauma, obesity, defined as a body mass index >25 kg/m², smoking, malignancies, hyperfibrinogenesaemia and age. Follow-up examinations were performed in 306 patients after 1–31 months (average 8 months). Two hundred and seven healthy volunteers (34% male, 66% women, average age 32 years) who were recruited among the employees of the University of Cologne served as a control group. In these individuals a genetic analysis was performed as described above. Statistical analysis was performed using SSPS statistical package, version 8.0 by SSPS Inc, Chicago, USA. To describe differences between non-parametric parameters chi-squared or Fisher’s exact test were used. Significance was regarded as p<0.05.

Results

Prevalence of APC-R

APC-R was found in 33 of 311 patients with arterial diseases (11%). In 12 patients a genetic analysis was added which revealed 11 heterozygote and one homozygote Factor-V mutation. Sixteen out of 207 healthy controls showed an APC-R (8%). In comparison to the study group this difference was not significantly (p=0.272). APC-R was equally distributed between male (25/228=11%) and female (8/83=10%) patients. APC-R affected 12% of the patients with PAOD (28/240) and 7% (5/71) of those presenting with an AAA (p=0.266). Twenty-one patients presented with an occluded previously implanted bypass, of which three had APC-R (14%). Among the remaining 290 patients 30 had APC-R (10%) (p=0.476).

Postoperative–postinterventional course

In 51 patients medical therapy was continued. Two hundred and sixty patients underwent surgical or endoluminal treatment, which was complicated by early thrombosis in five. The overall postoperative arterial thrombosis rate was 2% (5/231) and they all occurred in patients without APC-R. The five thrombotic complications all occurred after bypass operations (Table 2) resulting in a frequency of 6% in this subgroup. Twenty-nine other treated patients with APC-R did not show such complications. All bypass occlusions occurred in the early postoperative course (1st–13th day, mean 5th day). In four of the five cases an autologous bypass had been implanted (three femoro-infragenulate bypasses, one aorto-femoral bypass for infectious reason). In one patient a femoro-supragenulate PTFE graft occluded. None of the patients who experienced a bypass occlusion were immobilized preoperatively or suffered from trauma. Bypass occlusions did not occur more frequently in patients who were obese or who smoked. One out of 12 patients who had malignant disease suffered from bypass occlusion, but did not have APC-R.

Serum level of fibrinogen was elevated (>3.5 g/l) in 210 patients of whom 151 were also smokers. Only two developed an arterial thrombosis. In these patients APC-R could not be found.

Follow-up

During follow-up 301 patients were examined of which 257 had undergone surgery or endovascular treatment. Sixteen of these patients experienced an arterial or graft thrombosis (6%), of which two had APC-R (p=0.699). All incidences of thrombosis occurred in patients with PAOD and with an infragenulate distal anastomosis within 1–24 months after the intervention (mean 1 month).

Table 1. Performed procedures

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bypass</td>
<td>82</td>
<td>26.4</td>
</tr>
<tr>
<td>Embolectomy</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Desobliteration+ patchplasty</td>
<td>71</td>
<td>22.8</td>
</tr>
<tr>
<td>Endoluminal treatment</td>
<td>47</td>
<td>15.1</td>
</tr>
<tr>
<td>Aneurysm repair</td>
<td>42</td>
<td>13.5</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>10</td>
<td>3.2</td>
</tr>
<tr>
<td>Amputation</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>None</td>
<td>51</td>
<td>16.4</td>
</tr>
<tr>
<td>Total</td>
<td>311</td>
<td>100</td>
</tr>
</tbody>
</table>

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Discussion

APC-R in the general population

APC-R based on Factor V-Leiden mutation is the most important hereditary factor in the etiology of venous thrombosis.\textsuperscript{14–16} In the normal population APC-R occurs less frequently, but with a geographical distribution. In the present study the prevalence of APC-R in healthy volunteers was found to be 8%. This figure is comparable to other epidemiological studies performed in Germany.\textsuperscript{17} However, in Sweden and Greece for example a prevalence of more than 10% is documented whereas in other European regions (France, UK, Spain, Italy) it is approximately, 3%.\textsuperscript{18} Moreover, racial differences have been shown. In the USA APC-R varies between the black and white population substantially (1.4 vs 5.4%). Interestingly, this kind of thrombophilia is practically unknown in Africa, China and Australia,\textsuperscript{19} and the reason for that is obscure, but it is argued that all individuals exhibiting APC-R descend from a common ancestor.\textsuperscript{20} Furthermore, APC-R represents a selection advantage in human evolution since it protects the affected person from major blood loss, in particular under gynaecological or obstetrical circumstances.\textsuperscript{21} Lindquist\textsuperscript{22} reports that women with APC-R have a reduced risk of bleeding during pregnancy when compared with women without this genetic defect.

APC-R in arterial diseases

The prevalence of APC-R among patients with arterial disorders is unclear. Some authors state an increase incidence in younger patients,\textsuperscript{23,24} suffering from myocardial infarctions, strokes or other arterial thrombosis.\textsuperscript{25,26} Others do not support such an association.\textsuperscript{27} We could not confirm an increased prevalence of APC-R in patients with PAOD or AAA. Patients with PAOD showed a slightly increased APC-R rate in comparison to those with AAA (12 vs 7%). This trend might become clearer in larger trials with greater patient numbers. In this study, the prevalence rates might have been diluted because the study group was investigated by performing a functional test (the APC-ratio) in contrast to a primary genetic analysis in the control group. However, the additional genetic test in 12 patients with a pathological APC-ratio revealed a sensitivity and specificity rate of 100%. As the reliability of this test is generally supported, the presented results seem to describe true proportions.\textsuperscript{28}

APC-R in previous bypass occlusion

Only three out of 21 patients who were treated for an occluded bypass implanted in the past showed APC-R. Two of them had undergone surgery four times. In the third patient a bypass procedure had been performed only once. There were even patients in whom more than 10 operations had been performed so far and who did not have APC-R. The relatively small number of affected patients precludes definite conclusions regarding the association between previous graft thrombosis and APC-R.

APC-R in postoperative bypass occlusion and during follow-up

As part of the perioperative anticoagulation regimen, antiplatelet medication is continued. Postoperatively, low molecular heparin was given routinely in a dose double that of the standard recommendation for venous thrombosis prophylaxis.

All graft occlusions occurred in the early postoperative period in mainly distal bypasses using greater saphenous vein. None of these patients were shown to have APC-R, and these complications likely resulted from technical faults, which are comparatively frequent in peripheral autologous reconstructions.

The literature provides inconsistent information regarding this topic. Whereas in some publications the prevalence of APC-R among patients experiencing postoperative graft occlusion is increased,\textsuperscript{29,30} others
were unable to detect APC-R as a definite risk factor for bypass failure. We were unable to show any association between graft failure and APC-R; however, the limited number of outcome events reduces the power of our analysis. APC-R did not seem to play a significant role in graft failure during long-term follow-up. All occlusion occurred in infrageniculate bypasses. The prevalence of APC-R did not differ in patients with (12.5%) or without (11%) failure of the arterial reconstruction during follow-up. Likewise, only 7% (2/29) of patients with APC-R developed an occlusion which is comparable to an occlusion rate of 6% in all other patients without APC-R (14/228).

References


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