Activated Coagulation in Patients with Shock due to Ruptured Abdominal Aortic Aneurysm

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Background. Ruptured abdominal aortic aneurysm is associated with a high operative mortality. Postoperative thrombosis related complications are common, a possible mechanism being activation of the coagulation system and endothelial stimulation. The aim of the present study was to investigate the coagulation activity preoperatively in patients with ruptured and nonruptured abdominal aortic aneurysm in relation to the clinical outcome with special regard to the influence of shock.

Methods. Ninety-five patients with repair of infrarenal aortic aneurysm and forty-one controls without aneurysm matched by age, gender and smoking habits were studied. Thrombin-antithrombin (TAT), prothrombin fragment 1 + 2 (F1 + 2), and von Willebrand factor antigen (vWFAg) were measured.

Results. There were significantly higher levels of TAT, F1 + 2, and vWFAg in patients operated for ruptured compared to nonruptured abdominal aortic aneurysm. The highest level of TAT and F1 + 2 were detected in patients with rupture and shock.

Conclusion. The present data indicate a state of activated coagulation in patients with ruptured abdominal aortic aneurysm which is reinforced by shock.

Introduction

Despite advances in surgical and anaesthetic techniques the perioperative mortality remains high in patients with clinical shock due to a ruptured abdominal aortic aneurysm (rAAA). 1 The haemostatic response during elective operation for abdominal aortic aneurysm (eAAA) show extensive activated coagulation, and in patients with multiple trauma a state of hypercoagulation is well documented. 2,3 Little is known about the haemostatic changes during haemorrhage and shock in patients with rAAA. In a study by Davies et al. the coagulation activity was investigated preoperatively in patients with rAAA by a coagulation screen consisting of platelet count, prothrombin time, activated partial thromboplastin time, thrombin time and plasma fibrinogen concentration. 4 This study indicates that coagulopathy at admission predicts poor outcome in patients with rAAA. However, the authors suggested that more extensive laboratory studies are required to analyse the mechanisms that contribute to the development and persistence of coagulopathy in these patients. In two studies by Adam et al. patients with rAAA were investigated by plasma levels of thrombin-antithrombin complex (TAT) prothrombin fragment 1 + 2 (F1 + 2) as markers of thrombin generation. 5,6 These studies show elevated levels of TAT and F1 + 2 in patients with rAAA compared with nonruptured AAA indicating an ongoing coagulation activity.

In patients with rAAA shock at admission is a well-known poor predictor. A great majority of the deaths and complications in patients with rAAA are related to thrombosis. 4 Activation of the coagulation system is regarded as an important part of the thrombosis development. Hence, further investigation of the coagulation activity in relation to shock and complications in patients with rAAA is justified.

The aim of the present study was to investigate the coagulation activity preoperatively in patients with ruptured and nonruptured abdominal aortic
aneurysm in relation to the clinical outcome and for
the first time with special regard to the influence of
shock.

Material and Methods

The study was performed in accordance with the
principles of the Declaration of Helsinki and was ap-
proved by the regional ethics committee. Patients (or
in some cases the relatives) and control subjects
gave their approval in a written informed consent.
Controls and patients were from the same geographic
area and had similar socio-economic backgrounds.

AAA patients

Patients with co-existing malignant disease, uraemia,
or who had had a recent episode of thromboembolic
disease or a course of anticoagulant therapy were
excluded.

Fifty-five patients with ruptured infrarenal
abdominal aortic aneurysm (rAAA) were included.
All patients had a retroperitoneal haematoma and
43 had signs of clinical shock (or at least one episode
of hypotension prior to aortic cross clamping). The
remaining 12 patients were not in clinical shock.
Shock was defined as a systolic pressure of
<80 mm Hg.7 At our department all patients with
rAAA are clamped supraceliacally. No blood trans-
fusions were given before laparotomy and in accor-
dance with Crawford no significant attempt was
made for blood volume resuscitation until surgery.8
The transfusion policy at surgery included rapid
administration of large numbers of red blood cells
(RBC) units, along with sufficient plasma and plate-
lots to treat or prevent coagulopathy. RBC and plasma
units were given alternately until 10 units of each
were transfused, followed by a unit of aphaeresis
platelets in a massive transfusion situation.9 Coagul-
opathy was avoided by prevention of hypothermia
and correction of acidosis. Postoperative complica-
tions were recorded. Non-survivors were defined as
all dead within 30 days or not discharged alive.

Forty patients with an elective operation for non-
ruptured infrarenal aortic aneurysm (eAAA) were
also included.

Controls

The control group was selected in accordance with the
guidelines given by Grimes and Schulz.10 Several stud-
ies have established male gender, age, smoking and
a positive family history of AAA as independent risk
factors for AAA.1 A control group of volunteers with normal infrarenal aortic
diameter (<30 mm) were matched to the AAA patients
according to age, gender and smoking habits. Smoking
was defined as current smoking at the time of inclusion.

Imaging

The largest aortic diameter was measured using the out-
nermost ultrasonography reflection with the transducer
parallel to the longitudinal axis of the infrarenal aorta.
An abdominal aortic aneurysm was defined as an aorta
with an infrarenal diameter greater than 30 mm.1

Blood sampling and assays

Peripheral venous blood samples were taken from
controls and each patient preoperatively, and before
any blood products had been transfused. Samples
were centrifuged within 30 min at 2000 g for 20 min
and aliquots of plasma were frozen and stored
at −70 °C until analysis.

Using ELISA-kit levels of thrombin-antithrombin
(Enzygnost TAT micro, Dade Behring AG, Marburg,
Germany), and prothrombin fragment 1 + 2 (Enzygnost
F 1 + 2 micro, Dade Behring AG, Marburg, Germany)
were measured. The concentration of von Willebrand
factor antigen (vWFAG) was analysed by an ELISA (As-
serachrom vWF, Diagnostica Stago, Asnieres, France).
Haematocrit (Hct), platelet count, activated partial
thromboplastin time (aPTT), and prothrombin time
(PT) transformed to the International Normalized Ratio
(INR), were analysed by routine clinical methods.

Statistical analysis

All analyses were carried out using SPSS® statistical
software 14.0 for Windows™ (SPSS, Chicago, Illinois,
USA). Data are presented as the median(interquartile
range). Differences in findings between study groups
were assessed by Chi-square tests (two-tailed without
Yates correction) for discrete variables and by Mann-
Whitney tests for continuous variables. A p-value < 0.05
was considered significant.

Results

There were no significant differences between the con-
trols and the both AAA groups according to age, gen-
der and current smoking habits (Table 1). As shown in
Table 1 the diameter of the aneurysm in the ruptured
patient group was larger than in the non-ruptured
AAA patient group (p-value = 0.011). There were no
significant differences between patients with eAAA
and rAAA according to age, gender and current
smoking habits. As shown in Table 1 the diameter of
Table 1. Age, gender, current smoking habits and abdominal aortic diameter in controls and AAA patients. Values presented as median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 41)</th>
<th>eAAA (n = 40)</th>
<th>rAAA (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72(67–79)</td>
<td>71(63–78)</td>
<td>73(70–79)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>33/8</td>
<td>35/5</td>
<td>44/11</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>18(44%)</td>
<td>19(48%)</td>
<td>22(40%)</td>
</tr>
<tr>
<td>Aneurysm diameter (mm)</td>
<td>&lt;30</td>
<td>60(52–71)</td>
<td>73(60–80)</td>
</tr>
</tbody>
</table>

Table 2. Laboratory results in controls and AAA patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 41)</th>
<th>eAAA (n = 40)</th>
<th>rAAA (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (%)</td>
<td>42(39–43)</td>
<td>41(39–43)</td>
<td>36(28–40)</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>207(177–238)</td>
<td>216(176–242)</td>
<td>185(138–230)</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>30(26–35)</td>
<td>31(26–34)</td>
<td>28(24–33)</td>
</tr>
<tr>
<td>PT/INR</td>
<td>1.0(1.0–1.1)</td>
<td>1.1(1.0–1.1)</td>
<td>1.2(1.1–1.3)</td>
</tr>
<tr>
<td>TAT (µg/L)</td>
<td>2.9(2.1–3.9)</td>
<td>6.0(3.8–9.1)</td>
<td>45.9(31.7–77.5)</td>
</tr>
<tr>
<td>vWFag (%)</td>
<td>0.8(0.6–1.0)</td>
<td>0.8(0.6–1.1)</td>
<td>4.4(2.5–5.7)</td>
</tr>
<tr>
<td>vWF (µmol/L)</td>
<td>150(125–165)</td>
<td>154(138–176)</td>
<td>185(146–246)</td>
</tr>
</tbody>
</table>

Median and interquartile ranges. Mann-Whitney U test. NS = Non-significant; *p < 0.05; **p < 0.01 and ***p < 0.001 compared with control group value.

Table 3. Laboratory results for the two subgroups (with or without shock) of rAAA. Median and interquartile ranges. Mann-Whitney U test

<table>
<thead>
<tr>
<th></th>
<th>Ruptured AAA with shock (n = 43)</th>
<th>without shock (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAT (µg/L)</td>
<td>52.3(39.8–99.7)</td>
<td>18.3(12.0–36.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F1 + 2 (nmol/L)</td>
<td>4.58(3.60–5.82)</td>
<td>2.69(1.45–3.90)</td>
<td>0.011</td>
</tr>
<tr>
<td>vWFag (%)</td>
<td>139(167–243)</td>
<td>182(187–260)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

the ruptured AAAs was larger than the non-ruptured AAAs (p-value = 0.011). The laboratory results in Table 2 show no significant difference between the control group and patients with an elective operation for an infrarenal AAA, except for TAT. In patients with rAAA, Hct and platelets were significantly lower than in the eAAA group. There was no significant difference between patients with eAAA and rAAA in aPTT, but PT was significantly higher in the group with rupture. The values were, however, within the normal reference ranges (reference range as 95% confidence interval). TAT, F 1 + 2, and vWFag were all significantly higher in the rAAA than in the eAAA group. As shown in Table 3 there were significant differences in TAT and F 1 + 2 between patients with and without shock, with the higher values in shocked patients. In the group rAAA there were no significant differences in F1 + 2 and vWF between survivors (n = 43) and non-survivors (n = 12). The TAT concentration was 42.5(26.6–59.6) in survivors and compared with non-survivors, 60.2(47.0–121.5), there was a significant difference (p = 0.039). In the patient group with rAAA and shock 12 patients died, the main cause of death was multiple organ failure (Table 4). The major complications in survivor with ruptured AAA are shown in Table 5.

Discussion

Bleeding is a common problem in clinical surgery. The normal haemostatic system limits blood loss by a precisely regulated interaction between components of the vessel wall, circulating blood platelets and coagulation factors. For haemorrhage due to ruptured infrarenal abdominal aortic aneurysm the treatment is urgent intervention, most often surgery.

As untreated rupture is fatal, survival is dependent upon surgery. The mortality in these patients is still high. The outcome of the surgery is a complex process depending for instance on postoperative thrombosis related complications such as multiple organ failure, myocardial infarction, and thromboembolism. A possible mechanism for these complications is the activation of the coagulation system and endothelial stimulation. One key component in blood coagulation is thrombin. Thrombin induces local haemostasis by activating platelets and by converting fibrinogen to fibrin. The platelet aggregate with polymerized fibrin form a thrombus at the site of vascular injury. In the present study the plasma levels of thrombin-antithrombin complex (TAT) and prothrombin fragment 1+2 were assayed as markers of thrombin generation and thus TAT and F 1+2 reflect ongoing coagulation activity. The level of coagulation markers are known to depend on age and smoking habits and for that reason we used a control group matched by age and smoking habits to the AAA patient group. This study verifies results from previous studies suggesting a state of activated coagulation preoperatively in patients operated on for non-ruptured infrarenal aortic aneurysm. We also find significantly higher levels of TAT and F 1+2 in patients operated on for ruptured compared to...
nonruptured AAA. Furthermore the highest level of TAT and F 1 + 2 were detected in the patients with rupture and shock. The activation in patients with nonruptured AAA could reflect the thrombotic process within the aneurysmal sack, which is almost always seen. The further activation at rupture could reflect the response to bleeding, which, together with fall in blood pressure and counterpressure from the retroperitoneal tissue, could lead to preliminary haemostasis for hours before the next and usually fatal rupture occurs.

Modern management of the patient with haemorrhage due to ruptured AAA included rapid administration of large numbers of RBC, along with sufficient plasma and platelets to treat or prevent coagulopathy. Furthermore, aggressive re-warming to prevent hypothermia by warm fluid infusion, forced-air warming, and the use of warm water on the surgical field also prevent coagulopathy. Correction of acidosis also has a high priority during the initial evaluation.

In our patients with rAAA only 2 patients have fatal coagulopathy and bleeding. The main causes of death were multiple organ failure and cardiac failure. Adam et al. concluded that the procoagulant state in patients with rAAA may contribute to microvascular and macrovascular thrombosis that, in turn, lead to the common causes of perioperative morbidity and mortality, namely myocardial infarction, multiple organ failure, and thromboembolism. Our results show a relatively high incidence of thrombosis related complications and causes of death in patients with rAAA indicating a relation to the activated coagulation in these patients.

In conclusion our results indicate a state of activated coagulation in patients with AAA, the state being intensified by rupture and reinforced by shock.

Table 5. Major complications in survivor (n = 43) with ruptured AAA

<table>
<thead>
<tr>
<th>Major complications</th>
<th>n</th>
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<tbody>
<tr>
<td>Renal failure requiring haemodialysis</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory failure or pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>Acute myocardial infarction and/or cardiac failure</td>
<td>4</td>
</tr>
<tr>
<td>Distal embolism/thrombosis</td>
<td>4</td>
</tr>
<tr>
<td>Distal colonic ischemia requiring resection</td>
<td>1</td>
</tr>
<tr>
<td>Graft thrombosis requiring reoperation</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1</td>
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</tbody>
</table>

The results presumably explain the high incidence of thrombosis related events in AAA patients especially with shock due to rupture. The haemostatic response during elective operation for AAA is well documented and for these patients thrombosis prophylaxis is recommended. Our results seem to justify early thrombosis prophylaxis also in patients with ruptured abdominal aortic aneurysm, in an attempt to reduce the risk for thrombosis related complications.

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References


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