Changes in Platelet Count, Coagulation and Fibrinogen Associated with Elective Repair of Asymptomatic Abdominal Aortic Aneurysm and Aortic Reconstruction for Occlusive Disease

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Background: Mortality and morbidity following aortic surgery, particularly repair of ruptured abdominal aortic aneurysm (AAA), is frequently associated with the development of coagulopathy.

Objectives: To examine changes in platelet count (PC), fibrinogen, and coagulation in patients undergoing elective repair of asymptomatic abdominal aortic aneurysm (AAA) and aortic surgery for occlusive disease.

Design: Prospective clinical study in a University Department of Vascular Surgery.

Patients: Thirty-three patients undergoing elective repair of asymptomatic AAA and 19 patients undergoing aortic surgery for occlusive disease.

Methods: Full blood count (FBC), clotting screen, and fibrinogen measured pre-operatively; 6, 12, 24, 48 h postoperatively; and thereafter as clinically indicated in 23 consecutive patients undergoing AAA repair (Group 1). Pre- and postoperative PC measured weekly for 4 weeks following operation in a further 10 consecutive patients undergoing AAA repair (Group 2) and perioperative PC measured in 19 consecutive patients undergoing aortic surgery for occlusive disease (Group 3).

Results:

Group 1: Preoperative haematological parameters were normal. There was no mortality. Postoperatively, 21 (91%) patients developed thrombocytopenia (PC <150 x 10^9/l). The postoperative fall in PC (median 90, range 12–160 x 10^9/l) was significantly related to the duration of aortic cross-clamp (median 46, range 20–127 min, r^2 = 0.33, p<0.01). At 10 days all patients had developed thrombocytosis (PC >350 x 10^9/l). Postoperatively, by 48 h, 17 (74%) patients had developed hyperfibrinogenaemia. One patient suffered a myocardial infarction associated with a PC of 105 x 10^9/l and a fibrinogen of 7.2 g/l.

Group 2: In a further 10 patients undergoing AAA repair postoperative thrombocytosis was found to persist for several weeks in five of nine survivors.

Group 3: Patients undergoing aortic surgery for occlusive disease had significantly higher preoperative PC than AAA patients (median 292, range 179–251 x 10^9/l vs. median 204, range 140–239 x 10^9/l, p<0.01).

Conclusions: Patients undergoing elective repair of AAA demonstrate similar, albeit less dramatic, changes in platelet count to those we have previously reported in patients undergoing repair of ruptured AAA. Aortic clamping leads to platelet sequestration and thrombocytopenia in the early postoperative period. Later, patients develop hyperfibrinogenaemia and thrombocytosis which may persist for several weeks. Similar changes are seen in patients undergoing aortic surgery for occlusive disease. These changes may represent a hypercoagulable state that predisposes these patients to thrombotic complications.

Key Words: Aortic aneurysm; Aortic surgery; Platelet count; Fibrinogen; Coagulopathy.

Introduction

The great majority of patients dying after attempted repair of ruptured abdominal aortic aneurysm (AAA) do so from one or more of the following: continued haemorrhage, multiple-organ failure (MOF), thromboembolic disease (TED), and myocardial infarction (MI).

There is increasing evidence that disseminated intravascular coagulation (DIC), with its haemorrhagic and prothrombotic effects, is central to the pathogenesis of these important complications. In relation to patients presenting with ruptured AAA we have reported previously that established coagulopathy on admission to hospital is associated with a 100% mortality.1 In addition, we have demonstrated a close relationship between changes in perioperative platelet count (PC) and outcome.2 Thus, many patients develop a profound thrombocytopenia early in the postoperative
course that is strongly associated with death and mor-
bidity from continued haemorrhage. Later, ap-
proximately 50% of patients develop a thrombocytosis
which is associated with MOF, TED such as deep
venous thrombosis (DVT) and pulmonary embolism
(PE), and MI. The cause(s) of these changes in co-
agulation and PC are unknown. However, thrombus
within the aneurysm sac may lead to consumption
of platelets and coagulation factors such that these
patients already have a sub-clinical chronic DIC prior
to rupture. It has also been suggested that the fib-
rinolytic system is inappropriately activated in these
patients. Shock and ischaemia developing suddenly as
a result of rupture, and exacerbated by aortic clamping,
may therefore act on a “primed” haemostatic system
such that these patients rapidly develop a profound
cogulopathy that is out of proportion to the degree
of hypotension and blood loss. In order to understand
better the pathogenesis of DIC in patients undergoing
operation for ruptured AAA it is important to define
the situation with regard to elective aortic surgery.
The aim of the present study was therefore to examine
closely the changes in PC and coagulation associated
with elective aortic surgery for aneurysmal and oc-
clusive disease; and to correlate the changes observed
with morbidity and mortality.

Patients and Methods

Study group 1: Short term changes in PC, coagulation,
and fibrinogen following elective AAA repair

Twenty-five consecutive patients due to undergo elective
repair of asymptomatic AAA were prospectively studied. Two patients did not undergo aneurysm re-
pair; one was found to have a caecal mass at lap-
arotomy and underwent right hemicolectomy; the
other was found to be inoperable due to dense ad-
hesions from previous surgery. Data from 23 patients
were therefore available for study. In each patient full
blood count, activated partial thromboplastin time
(APTT), prothrombin time (PTR), and fibrinogen were
measured preoperatively and at 6, 12, 24, 48 and
72 h postoperatively. Bloods were drawn thereafter as
clinically indicated. Information on operative time,
clamp time, blood loss, administration of heparin and
protamine, transfusion requirements, as well as details
of morbidity were prospectively documented.

Study group 2: Medium term changes in PC following
elective AAA repair

Because a proportion of patients in study group 1 had
been found to have a thrombocytosis persisting to
discharge from hospital a second group of 10 patients
undergoing elective AAA repair were followed-up
prospectively after discharge in order to determine
how long thrombocytosis might persist.

Study group 3: Short term changes in PC following
elective aortic reconstruction for occlusive disease

In order to determine whether the observed changes
in PC were specific for AAA surgery a consecutive
group of 19 patients undergoing aortic reconstruction
for occlusive disease were also studied. There were 14
men and five women with a median age (range) of 62
(42–85) years.

Results

Study group 1: Short term changes in PC, coagulation,
and fibrinogen following elective AAA repair

The median age (range) of patients was 72 (53–84)
years. There were five women and 18 men. No patients
were receiving aspirin or non-steroidal anti-in-
flammatory drugs preoperatively. The median max-
imum diameter (range) of the AAA was 6.5 (4.3–8.3) cm
as measured by preoperative ultrasound examination.
Six patients required bifurcation grafts. All patients
received coated Dacron prostheses and between 3000
and 5000 units of heparin prior to aortic clamping.
There was no mortality. Morbidity comprised one
postoperative MI, one iatrogenic pneumothorax, one
episode of myocardial ischaemia without evidence of
infarction, a lymph leak from a groin wound and
five chest infections. One patient underwent a second
laparotomy for suspected ischaemic bowel but no
abnormality was found and the patient recovered
uneventfully thereafter.

The median duration (range) of surgery was 120
(60–240) min, the median duration (range) of aortic
cross-clamp time was 46 (20–127) min, and the median
blood loss (range) was 1285 (450–3210) ml. Pre-
operative haematological parameters (Table 1) were
not significantly deranged.

Postoperatively, 21 (91%) patients developed
thrombocytopenia (PC <150 × 10^9/L, normal range in
our laboratory is 150–350 × 10^9/L) during the first 72
postoperative hours (Fig. 1). Postoperative fall in PC
was defined as the difference between preoperative
PC and the lowest PC detected in the first 72 h post-
operatively. The postoperative fall in PC (median 90,
Elective Aortic Surgery, Coagulation and Platelet Count

Table 1. Preoperative haematological parameters in 23 patients undergoing elective repair of asymptomatic abdominal aortic aneurysm.

<table>
<thead>
<tr>
<th></th>
<th>Patient median (range)</th>
<th>Normal median (range)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/l)</td>
<td>13.4 (9.2-15.4)</td>
<td>M: 13-18, F: 11.5-16.5</td>
<td>NS</td>
</tr>
<tr>
<td>White cell count (x 10^9/l)</td>
<td>67 (5.0-8.8)</td>
<td>4-11</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count (x 10^9/l)</td>
<td>204 (160-293)</td>
<td>150-350</td>
<td>0.01*</td>
</tr>
<tr>
<td>Prothrombin time (secs)</td>
<td>12.1 (10.8-17.6)</td>
<td>control = 12</td>
<td>NS</td>
</tr>
<tr>
<td>Activated partial thromboplastin time(s)</td>
<td>33.4 (26.4-43.9)</td>
<td>control = 34</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>5.16 (2.61-4.0)</td>
<td>1.5-4.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Compared with a population of 19 patients undergoing aortic surgery for occlusive disease, Mann-Whitney test.

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range 12–160 x 10^9/l) was related significantly to the duration of aortic cross-clamp (median 46, range 20–127 min, r^2 = 0.33, p<0.01) (Fig. 2) but not to the total duration of operation, operative blood loss, transfusion requirements, preoperative PC, the amount of heparin or protamine administered, diameter of AAA, or the presence of iliac extension of aneurysmal disease. At 10 days all four patients who had not yet been discharged had developed thrombocytosis (PC >350 x 10^9/l).

There was no significant prolongation of clotting times preoperatively. There was a non-significant prolongation of both PTR and APTT in all patients postoperatively but by 72 h clotting times had returned to normal. The changes in APTT and PTR were not significantly related to clamp time, total operating time, operative blood loss, or transfusion requirements.

There was no significant abnormality in preoperative fibrinogen levels. Postoperatively, there was an early fall in fibrinogen but by 48 h 17 (74%) patients had developed marked hyperfibrinogenaemia (Fig. 3). There was no significant correlation between the increase in fibrinogen and aortic clamp time, total operating time, blood loss, transfusion requirements, preoperative fibrinogen or postoperative changes in PC.

One patient, a 72-year-old man, suffered an MI on the third postoperative day as demonstrated by new ECG changes and a rise in cardiac enzymes. Until
that point the patient had followed an uneventful perioperative course following Y-graft repair of a 7.7 cm aortobi-iliac aneurysm. The MI was associated with left ventricular failure which required readmission to the intensive care unit. He was treated with oxygen and nitrates and made a slow but otherwise uncomplicated recovery. This patients perioperative haematological parameters were normal. Infarction was associated with a thrombocytopenia of $105 \times 10^9/\text{l}$ and a markedly raised fibrinogen of 7.2 g/l (Fig. 4).

**Study group 2: Medium term changes in PC following elective AAA repair**

The median age (range) was 70 (65–78) years. PC was measured preoperatively; during postoperative hospital stay; and 2, 3, and 4 weeks after surgery. Four patients were taking aspirin prior to surgery and six patients received intraoperative heparin. The median operation time (range) was 110 (70–285) min and the median aortic cross-clamp time (range) was 38 (30–90) min. Six patients had bifurcated grafts inserted. The median operative blood loss (range) was 1250 (400–6000) ml and the median transfusion requirement (range) was 2 (0–13) units of red cell concentrate. All patients were commenced on subcutaneous heparin (5000 U twice daily) on the first postoperative day in the absence of clinical and/or laboratory evidence of abnormal coagulation or PC.

The median preoperative PC (range) was 198 (143–260) $\times 10^9/\text{l}$. Within the first postoperative week, PC fell significantly in all patients and six developed thrombocytopenia. One patient had a fatal MI on the third postoperative day which was associated with a PC of $142 \times 10^9/\text{l}$. During the second and third weeks, five of nine survivors developed thrombocytosis. At 1 month after surgery, PC was higher than preoperative levels in seven of nine patients at which point the median PC (range) was 207 (159–315) $\times 10^9/\text{l}$.

**Study group 3: Short term changes in PC following elective aortic reconstruction for occlusive disease**

The median preoperative PC (range) was 292 (179–251) $\times 10^9/\text{l}$ which fell to a median (range) of 187 (103–364) $\times 10^9/\text{l}$ during the first 24 h postoperatively ($p<0.001$ by Mann-Whitney test) (Fig. 5). Preoperative PC in the 33 patients undergoing AAA repair (median 204, range 140–293 $\times 10^9/\text{l}$) was significantly lower than preoperative PC in those patients undergoing aortic operation for occlusive disease ($p<0.05$ by Mann-Whitney U-test for unpaired samples). In other respects the postoperative pattern of PC resembled that seen in AAA patients although the changes were not as great.

**Discussion**

Although coagulopathy complicating ruptured AAA has received considerable attention, to date, few studies have examined the changes in coagulation associated with elective aortic surgery for either
aneurysmal or occlusive disease. Furthermore, in most studies, these two pathologies are not differentiated. Gibbs and colleagues found increased levels of fibrinogen, factor VIII, von Willebrand factor; no change in PTR, APTT, thrombin time, or platelet aggregability; and decreased protein C, antithrombin III and α2 macroglobulin 2, 4, and 6 days following aortic surgery. They concluded that patients undergoing aortic surgery may develop a postoperative hypercoagulable state that possibly predisposes to thrombotic complications such as MI. Similarly, Gomez et al. found a significant increase in platelet derived plasminogen activator inhibitor (PAI) after aortic surgery. De Mol Van Otterloo et al. found that patients with AAA demonstrated increased platelet activation and fibrin metabolism as shown by increased preoperative levels of β-thromboglobulin, fibrinopeptide A (FPA), and fibrin degradation products (FDP) when compared with patients undergoing cholecystectomy. Gallino et al. found that patients with AAA had increased urinary FPA suggesting increased thrombin formation. The present study is therefore the first to examine prospectively in detail the preoperative, short and medium term postoperative changes in PC and coagulation associated with elective aortic surgery for both aneurysmal and occlusive disease.

Preoperatively, patients exhibited no significant derangement in serum fibrinogen, APTT or PTR. Although AAA patients did have significantly lower PC than patients undergoing aortic surgery for occlusive disease, it is difficult to know whether this represents a relative reduction in PC in patients with AAA or a relative increase in PC in patients with occlusive aortoiliac disease. In other respects the postoperative changes in PC accompanying aortic surgery for occlusive disease were similar to those found after AAA repair.

Postoperatively, patients undergoing elective aortic surgery demonstrated similar, albeit less dramatic, changes in PC to those we have previously observed in patients undergoing emergency repair of ruptured AAA; that is, early thrombocytopenia and later thrombocytosis. Furthermore, follow-up studies in AAA patients suggest that these changes may persist for at least several weeks after operation. There was no relationship between blood loss and blood product replacement and fall in PC. Interestingly, however, there was a significant relationship between the period of aortic cross-clamp and the fall in PC during the first 72 h postoperatively. This phenomenon has not previously been reported in patients although Cohen et al. found a significant correlation between aortic clamp time and fall in PC in a canine model of supracoeliac aortic occlusion.

Taken together these results support the hypothesis that aortic cross-clamping contributes to platelet sequestration and thrombocytopenia in the early postoperative period. The mechanisms underlying this process, as well as the later development of thrombocytosis, are unknown but may be related to increased levels of circulating cytokines, in particular interleukin(IL)-6. Other workers have reported free radical mediated lipid peroxidation on reperfusion following supracoeliac aortic cross clamping as part of aneurysm repair. Gadala et al. studied 10 patients undergoing AAA repair and found a close relationship between aortic clamp time, neutrophil derived leukotriene B4 production, arterial oxygen pressure/inspired oxygen ratio on admission to the intensive therapy unit, and tracheal intubation time. Platelet count may therefore be a manifestation of a complex series of events involving platelet, leucocyte and endothelial cell activation. AAA repair would therefore seem to be an excellent model for looking at the mechanisms underlying ischaemia-reperfusion injury.

The present study also demonstrates that patients undergoing aneurysm repair develop postoperative hyperfibrinogenemia. Recent studies have indicated that hyperfibrinogenemia is a powerful, independent risk factor for cardiovascular, peripheral vascular and cerebrovascular disease; although the mechanisms involved are not fully understood. For example, in the Edinburgh Artery Study, serum fibrinogen was independently associated with the prevalence of both
asymptomatic and symptomatic arterial disease.\textsuperscript{15} Raised fibrinogen levels have been reported after urological,\textsuperscript{17} gastrointestinal,\textsuperscript{18} cardiac,\textsuperscript{19} and orthopaedic surgery for trauma.\textsuperscript{20} The causes of postoperative hyperfibrinogenaemia are not well defined but may, like changes in PC, be at least partly due to IL-6 stimulation of the liver.\textsuperscript{15} Fibrinogen may also be released by megakaryocytes and circulating platelets.\textsuperscript{21}

The clinical consequences of post-operative hyperfibrinogenaemia and changes in PC require further study but changes in fibrinogen and fibrinopeptide levels have been linked to the development of pulmonary dysfunction following trauma\textsuperscript{22} and to arterial bypass occlusion. In this respect fibrinogen is known to enhance leucocyte\textsuperscript{23} and platelet\textsuperscript{24} adherence to vascular endothelium. It is particularly interesting to speculate whether there might be an association between postoperative hyperfibrinogenaemia, platelet sequestration and MI. The single patient suffering an MI did so on the third postoperative day and at that time had a falling PC of 105 x 10\textsuperscript{9}/l and a rapidly rising fibrinogen level at almost twice the upper limit of the normal range at 7.4 g/l.

In general, elective aortic surgery is a safe procedure with a widely reported operative mortality of less than 5\%. Derangements in haemostatic mechanisms and coagulation are, therefore, for the most part subclinical. However, understanding the pathogenesis of these changes in elective aortic surgery is important if we are to improve further upon these results as well as to determine the causes of coagulopathy associated with emergency repair of ruptured AAA where the operative mortality is 10 to 20 times higher.

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References


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