Effects of Asymptomatic Abdominal Aortic Aneurysm on the Soluble Coagulation System, Platelet Count and Platelet Activation

A. A. Milne*1, D. J. Adam1, W. G. Murphy2 and C. V. Ruckley1

1Vascular Surgery Unit, University Department of Surgery, Royal Infirmary of Edinburgh, U.K.; 2Department of Medicine, University of Edinburgh, U.K.

Objectives: the aim of the study was to determine the effects of infrarenal asymptomatic abdominal aortic aneurysm (AAA) on platelet count and activation.

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

Patients: one hundred and five patients with AAA. Thirty-two control patients with symptomatic carotid artery stenoses.

Methods: platelet count (PC), plasma glycocalicin levels, prothrombin ratio (PTR), activated partial thromboplastin time (APPT), fibrinogen and D-dimer were measured in 23 patients with AAA and 16 control patients with symptomatic carotid artery stenoses. PC alone was measured in a further 84 patients with AAA and 16 with carotid artery stenoses.

Results: PC was below the normal range in 8/105 patients and mean PC (215 ± 109/l, s.d. 47.5) was significantly lower than that of a control population (242 ± 109/l, s.d. 16.8) and patients with carotid disease (269 ± 109/l, s.d. 57). Glycocalicin level was above the normal range in 7/23 patients and the median level (28 fg/plt) was significantly higher than that of a normal population (21.6 fg/plt) and patients with carotid disease (12.3 fg/plt). Fibrinogen levels, PTR and APPT were all within the normal range. One patient had a minimally elevated level of D-dimer.

Conclusions: the combination of low PC and high glycocalicin levels suggests that there is increased platelet destruction, most likely due to activation within the aneurysm sac.

Key Words: Aortic aneurysm; Haemostatic system; Platelets; Glycocalicin.

Introduction

It is well recognised that patients with ruptured abdominal aortic aneurysm (AAA) may develop a coagulopathy and that this is associated with a very poor prognosis.1 Subclinical abnormalities of the coagulation system have been reported in patients with non-ruptured aneurysms and there have been case reports of disseminated intravascular coagulation (DIC), attributed to the presence of an intact aortic aneurysm.2–5 It has been postulated that the coagulation system may be “primed” in patients with asymptomatic AAA and this may contribute to the development of a coagulopathy should rupture occur.6

The aims of this study were to determine, for the first time, the presence and degree of activation of platelets in a population of patients with asymptomatic AAA.

Patients and Methods

Twenty-three patients with a diagnosis of AAA were identified in the out-patient department. The diagnosis was confirmed by ultrasonography. The anteroposterior diameter was recorded, as were clinical details such as age, past medical history and drug history. The median age of patients was 69 years. The male: female ratio was 4.5:1. The mean aneurysm diameter was 48 mm (range 32–65 mm). Six patients were taking regular aspirin.

Blood samples were taken from an antecubital vein without tourniquet occlusion. A 5 ml sample was taken into EDTA for platelet count and a 5 ml sample was taken into citrate for glycocalicin, prothrombin ratio (PTR), activated partial thromboplastin time (APPT), fibrinogen and D-dimer. Glycocalicin assay was performed using an ELISA technique as previously described and levels were corrected for platelet count, as it has previously been shown that glycocalicin level is proportional to platelet count in a normal population.7

In addition to the above patients on whom complete
coagulation studies were performed, platelet counts were obtained from hospital records in a further 82 patients admitted for elective AAA repair.

The study group platelet counts were compared with mean values for a hospital population of 2000 consecutive samples and also with a group of 32 patients undergoing carotid endarterectomy for symptomatic carotid stenoses who were recruited as part of other studies. The median age of these patients was 67 years and the male to female ratio was 1.3:1. Twenty-nine of these patients were taking regular aspirin. Glycocalcin levels in 23 patients with AAA were compared with values for a normal population previously determined in this laboratory (mean 21.6 fg/plt, s.d. 8) and with 16 of the group of patients with symptomatic carotid stenoses.

**Results**

Platelet counts were in the lower part of the normal range and were below the normal range in 8/105 patients (Fig. 1). The mean platelet count was 215 × 10^9/l (s.d. 47.5). This was significantly lower than that of a control population of 2000 consecutive samples (mean platelet count 242 × 10^9/l, s.d. 16.8) – p<0.0001 by T-test and significantly lower than the patients with carotid disease (mean platelet count 269 × 10^9/l, s.d. 57) – p<0.001 by T-test.

In 7/23 patients levels of glycocalcin were above the normal range. The median plasma level of glycocalcin per platelet (28 fg/plt × 10^9) was higher than that of a normal population (21.6 fg/plt × 10^9) p = 0.001 and higher than that of patients with carotid disease (12.3 fg/plt × 10^9, s.d. 5.4) p = 0.0001 by Mann–Whitney (Fig. 2). All patients had plasma fibrinogen levels within the normal range, although these tended to be at the upper end of the range. One patient had a minimally elevated level of D-dimer and this was not associated with any other abnormality on coagulation screen. All patients had a PTR and APPT within the normal range. The platelet count, glycocalcin level and fibrinogen level did not correlate with size of aneurysm, age of patient or aspirin usage.

**Discussion**

The present study has shown that in patients with asymptomatic AAA the mean platelet count is about 10% lower than the control population and about 10% of patients have platelet counts below the normal range. These abnormalities cannot be attributed to the presence of generalised vascular disease; in fact, such patients would be expected to have higher than normal platelet counts, as found in the patients with carotid disease.

These low platelet counts are associated with high levels of glycocalcin. This is not simply a statistical phenomenon due to the lower platelet counts in the aneurysm group, as the absolute levels of glycocalcin are also higher. Glycocalcin is the extra-membranous portion of glycoprotein 1 (GP1b) produced when GP1b is cleaved from the platelet membrane. It is a marker...
of platelet activation and turnover. The elevated glyco-
calin levels found in patients with AAA cannot be
ascribed to generalised vascular disease; low levels of
glyocalcin have been reported in patients with peripheral vascular disease and ischaemic heart dis-
ease and, in the present study, patients with symp-
tomatic carotid artery disease had lower levels of
glyocalcin than AAA patients. Although aspirin
usage was more common in the patients with carotid
disease, this is unlikely to be the cause of this dif-
fERENCE, as we have previously shown that glyocalcin
levels are not affected by aspirin usage in normal
subjects. It would therefore appear that the presence
of AAA has a significant effect on platelets.

The present study did not reveal any significant
derangement of the soluble coagulation system, con-
trary to previous reports. There was no evidence of
excessive fibrinolysis or consumption of clotting fac-
tors as shown by the normal PTR, APPT and D-dimer
levels. Fibrinogen levels in all patients were within
normal limits but at the upper end of the normal
range, as would be expected in patients with vascular
disease. This negative finding may be due to the
relatively small size of aneurysms in the study group,
as the case reports of DIC have involved patients with
large aneurysms.

There are four possible mechanisms for the low
platelet counts in patients with AAA: decreased rate
of production, increased rate of destruction, platelet
sequestration, e.g. in the spleen, and dilution. Dilution
is unlikely, as this occurs when there is rapid expansion
of plasma volume. Likewise, there is no evidence for
sequestration, such as splenomegaly. Decreased rate
of platelet production seems unlikely, as these patients
are capable of producing a thrombocytosis following
surgery. Thus, an increased rate of destruction
seems the most likely cause of thrombocytopenia.

The simplest explanation is that platelets are ac-
tivated by the clot in the aneurysm sac, adhere and
become incorporated into the clot. GPIb is released at
the time of activation, accounting for the elevated
glyocalcin. This process might be termed “con-
sumption within the sac”. If this is the case, then the
remaining circulating platelets would have normal
surface expression of GPIb and function normally.
This hypothesis is supported by studies using radio-
labelling which have demonstrated that platelets and
fibrinogen are deposited in the clot within the an-
eurysm sac. A similar pattern of low platelet counts
and high glyocalcin levels has been described in
patients with rheumatic valve disease and was at-
tributed to platelet activation on the damaged valves.

However, the situation may be more complex. Plate-
lets have a normal life span of about ten days, but the
ageing process which marks them for destruction is
poorly understood. It is known that coming into con-
tact with a foreign surface, such as subendothelium,
can activate platelets and such platelets are cleared
from the circulation regardless of their age. Such
activation of the platelet without adhesion may occur
within the aneurysm sac, producing changes to the
circulating platelet which mark it for early destruction.
The elevated glyocalcin levels may then be accounted
for by one of two mechanisms. It may simply be that
GPIb is released at the time of platelet destruction in
the reticuloendothelial system. The other explanation
concerns the mechanism by which platelets are marked
for early clearance from the circulation. It has been
proposed that platelets undergo gradual loss of GPIb
throughout their life span and that this is the means
by which senescent platelets are identified by the
reticuloendothelial system. It has been demonstrated
in vitro that activation of platelets can lead to the
generation of a protease which cleaves GPIb close to
the site of its insertion onto the platelet membrane.
Thus it may be that activation within the sac causes
release of GPIb, marking the platelet for early clear-
ance. If this is the case, there may be circulating
platelets which are deficient in GPIb receptors.

GPIb is central to the process of platelet adhesion
at the site of vessel wall injury and thus vital for clot
formation and haemostasis. It is therefore easy to
envisage that platelets deficient in GPIb would be
dysfunctional. Such loss of GPIb occurs during platelet
storage in blood banks and has been proposed as the
reason for the decreased functional ability of stored
platelets. Thus, in these patients there may be a
combination of dysfunctional platelets and a mild
degree of thrombocytopenia which could significantly
compromise the coagulation system. Haemostatic
function in the resting state might be near normal, but
the threshold at which clinical bleeding problems occur
would be much lower, and there would be little reserve
in the face of a major challenge to the haemostatic
system such as aneurysm rupture or aortic operation.

In order to resolve these questions, more detailed
studies of expression of cell surface receptors are
required, using techniques such as flow cytometry.
Such studies would not only provide information
about platelet function in these patients but may also
help to explain the mechanism by which senescent
platelets are identified and destroyed by the reticulo-
endothelial system.

Acknowledgements

We would like to thank staff at the coagulation laboratory of the
South East Scotland Blood Transfusion Service for carrying out the
coagulation tests.
Effects of Asymptomatic AAA on Platelet Count and Activation

References


19 Bessos H, Murphy WG, Robertson A et al. Quality of platelet concentrates irradiated with AVB light: effect of dose and dose rate on glycocalcin release and correlation with other markers of the platelet storage lesion. Transfusion Medicine 1993; 3: 115–121.

Accepted 2 December 1998

Eur J Vasc Endovasc Surg Vol 17, May 1999