The irrelevance of adhesive platelet estimations after thrombosis

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SYNOPSIS It has been found that adhesive platelet counts are not of clinical use either after surgical operation or during long-term anticoagulant therapy in the detection of thrombosis. Calculation of the theoretical risk of development of platelet thrombi related to the platelet count suggests a possible reason for this absence of clinical significance. The evidence that platelet adhesiveness alters because of uncontrollable platelet variables and is controlled at least in part by plasma factors is discussed. The possibility of measuring the plasma factors is considered briefly.

Estimation of platelet adhesiveness has not been found to be clinically useful either during long-term anticoagulant therapy (Eastham, 1966; Eastham and Avis, 1966) or in the detection of venous thrombosis after surgery (Negus, Pinto, and Brown, 1969). A reassessment of this absence of obvious clinical significance has now been attempted, as there is evidence that the degree of platelet adhesiveness can change rapidly without any variation in the total platelet count, and because it now appears that platelet adhesiveness is greatly influenced by plasma factors (Bennett, 1968; Besterman, Myat, and Travadia, 1967; Bolton, Hampton, and Mitchell, 1967).

Methods and Materials

Total platelet counts and adenosine diphosphate (ADP)-induced adhesive platelet counts were performed on a total of 650 blood samples from six male volunteers and from 57 patients during long-term anticoagulant therapy over a period of six to 24 months, using the methods of Eastham (1963 and 1964). The patients studied included two men with mitral valve stenosis and attacks of embolism, eight men and one woman with deep vein thrombosis and a history of attacks of pulmonary embolism, and 45 men and one woman who had suffered from myocardial infarction. All these patients were being treated with oral anticoagulants.

In addition, total and adhesive platelet counts were obtained daily from a 24-year-old woman suffering from idiopathic thrombocytopenic purpura, who underwent spienectomy to relieve this condition.

Results

The mean adhesive platelet count for the whole group was 56% (1 SD = 8·8%) of the total platelet count. Mean values for the adhesive platelet counts in the six volunteers not taking oral anticoagulants (54·5%), nine patients with venous thromboses (55·2%), and 46 patients following myocardial infarction (56·2%) were not significantly different from the total mean value. Pegrum, Shaw, and Wolff (1967), using the same method, obtained a mean value of 60·5 ± 6·35% from 67 normal control subjects. This result is significantly different from the mean value for these patients on oral anticoagulants (p < 0·01).

There is a direct correlation between the mean
total platelet count and the mean adhesive platelet count in the 63 subjects (Fig. 1). When the highest
and lowest adhesive platelet counts found in each subject are plotted against the corresponding
mean total platelet count (Fig. 2), it can be seen that most of the maximum values fall within 60
to 80%, and most of the minimum values fall within 20 to 40% of the corresponding total
platelet counts, the results showing a regular distribution (Eastham, 1966). No clinical condi-
tion was found to account for either very high or very low adhesive platelet counts. As reported
previously (Eastham, 1966), the total platelet count in each case varied over the period of study
by an average of ± 10 to 15%, and the correspon-
ding adhesive platelet count varied by an average of ± 25 to 30%.

Results obtained from the 24-year-old woman treated by splenectomy for idiopathic thrombo-
cytopenic purpura are shown in Figure 3. Before splenec-
tomy the whole blood platelet count was
persistently below 15,000 per cmm. After sple-
ecotomy the whole blood platelet count rose during
the first seven days to exceed 500,000 per cmm
and during this period the adhesive platelet count
also increased but fluctuated markedly. By the
fourteenth day after operation clinical signs of
pulmonary embolism were obvious with clinically
detectable venous thrombosis in either leg.

Discussion

Evidence that platelets play an important part in
the development of atherosclerosis and arterial
thrombosis has been reviewed (Eastham, 1966).
Unfortunately no useful prognostic value was
obtained from total or adhesive platelet counts
during long-term oral anticoagulant therapy
(Eastham, 1966; Eastham and Avis, 1966). In any
individual the total platelet count has been shown
to vary about a mean value by an average of 10
to 15% and the corresponding ADP-induced
adhesive platelet count to vary by an average of
25 to 30% (Eastham, 1966). It is obvious that
the adhesive platelet count cannot exceed 100%.
Re-examination of the latter results shows that
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There is evidence that platelet adhesiveness is controlled by plasma factors, and Besterman et al (1967) were able to demonstrate a diurnal variation in the adhesive platelet count, probably due to the normal diurnal variation in circulating adrenaline and noradrenaline, without a corresponding variation in the total platelet count. (Catecholamines such as adrenaline and noradrenaline release ADP from the platelet surface.) Further evidence of humoral control of platelet adhesiveness, either with added ADP or without added ADP, is that platelet adhesiveness increases within four hours of surgical operation, especially when the method of estimation includes erythrocytes from the patient (Bennett, 1968), and it is of interest that platelet adhesiveness and red cell electrophoretic migration rates are directly correlated (Davies and Lloyd, 1967). Similarly plasma obtained from subjects after exercise or stress shows that these factors grossly enhance platelet aggregation (Harrison, Emmons, and Mitchell, 1967). Although ADP is released from platelets, paradoxically platelets also carry enzymes for the elimination of circulating ADP and this platelet ‘ADP-ase’ system is enhanced by a heat-stable plasma factor (Howe and Bosshardt, 1968). It also appears that a lysolecithin, released from low-density lipoprotein by a plasma lecithinase, is responsible for marked changes in platelet electrophoretic mobility in response to ADP in patients suffering from arterial disease (Bolton et al, 1967).

The fluctuating rise in adhesive platelets which accompanied the thrombocytosis following splenectomy for idiopathic thrombocytopenia (Fig. 3) could be explained by the presence of factors affecting the development of adhesiveness in platelets, with unpredictable numbers of such platelets trapped in an unsuspected developing deep vein thrombosis and in the subsequent pulmonary embolism. Following the demonstration of the development of a stage where platelets are refractory to ADP (Rozenberg and Holmsen, 1968) it is suggested that the estimation of adhesive platelets by any method could be inefficient in demonstrating the presence of factors causing increased platelet adhesiveness.

It is possible that it might be better to estimate the zeta potential at a standard glass-plasma interface, since this measurement would correlate with the zeta potential at the platelet surface, and hence with the platelet adhesiveness, which increases with decrease in the negative surface charge and its electrophoretic mobility (Dawber and Roberts, 1968). The relationship between fall in zeta potential and aggregation of particles in human plasma has been investigated by Gardner (1969) who demonstrated that the normal state is unstable with zeta potential in the order of magnitude of threshold agglomeration of erythrocytes. By avoiding direct measurements on platelets in this way, more delicate estimations of
factors liable to increase the risk of thrombosis may become possible.

The risk of thrombosis in a vessel with an arteriosclerotic plaque on its wall is impossible to assess, but certain theoretical calculations are possible. The number of platelets flowing in blood with a platelet count of 250,000 per cmm, through a small coronary artery of 2 mm internal diameter at a rate of 40 cm per second, is approximately $3 \times 10^8$ platelets per second. It is therefore not surprising that platelet thrombi can develop rapidly on such a patch. On the other hand, the wide spread of values for adhesive platelets (Fig. 3) have not been found to be clinically useful, and it is not difficult to offer an explanation. With eddy currents swirling and branching in smaller arteries, the blood will tend to be fully mixed, and coaxial flow will probably not occur. The risk of impact of platelets on a plaque will therefore be proportional to the cube root of the platelet count. Assuming platelet counts of 15,600, 125,000, 422,000, and 1,000,000 per cmm the order of risk of impact would be 25:50:75:100 or 1:2:3:4 only. The absence of clinical correlation with adhesive counts ranging from 30,000 per cmm to 240,000 per cmm in this series corresponds to a risk ratio of only 1:2 at the greatest difference found, if this suggestion is valid.

The estimation of the adhesiveness of platelets is clinically of value in the detection and classification of bleeding conditions associated with defective platelets, such as thrombocytasthenia (Glanzmann’s disease), thrombopathia, and von Willebrand’s disease.

References


