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Bleeding Time and Platelet Volume in Acute Myocardial Infarction – A 2 Year Follow-Up Study

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Key words

Acute myocardial infarction – Bleeding time – Platelets – Platelet volume

Summary

The bleeding time is shortened and the mean platelet volume is increased in the acute phase of myocardial infarction. In this follow-up study we repeated the measurement of the bleeding time, the platelet count and the platelet volume distribution in 18 patients who had suffered from a definite acute myocardial infarction two years before and in 16 control patients who had been admitted with chest pain but no definite myocardial infarction at that time. At the time of follow-up the bleeding time was significantly lengthened in the myocardial infarction group (median values = 169 s and 209 s respectively), whereas it had shortened in the control group (median values = 258 s and 228 s respectively). Comparison of the platelet volume distribution curves of the myocardial infarction patients at time of infarction and 2 years later revealed a significantly higher percentage of small platelets and significantly lower percentages of both medium-sized and large platelets at the time of infarction. These changes in the platelet volume distribution could indicate consumption of medium-sized and large platelets at the time of myocardial infarction. None of the measured variables predicted which of the patients with acute myocardial infarction would subsequently re-infarct or die. In the patients studied with definite ischaemic heart disease (n = 26) a significant negative correlation between bleeding time and mean platelet volume was found. The shortened bleeding time in myocardial infarction is related to the acute event itself or preceeds it, but is reversed two years later.

Introduction

Platelets and their interaction with the vessel wall are believed to be of importance in the development of atherosclerosis and its complication arterial thrombosis (1, 2). Since large platelets are more active haemostatically than small ones (3, 4), the reported increased mean platelet volume in acute myocardial infarction (5, 6) may be related to the occurrence of the arterial thrombus. However, it has been suggested that the increase is due to consumption of small platelets during the infarction (7); pointing to an effect rather than a cause of the infarction.

The bleeding time is generally accepted as the best indicator of the platelet-vessel wall interaction (8). Recently we have reported that the bleeding time is shorter in patients with definite acute myocardial infarction than in patients with chest pain but no definite acute myocardial infarction (9).

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In order to elucidate whether the observed decrease in the bleeding time during the acute phase of the myocardial infarction was still present 2 years later we performed a follow up study. The platelet volume distribution and the platelet count were also measured to investigate if any changes in these variables had occurred and to assess their ability to predict a fatal outcome or a new acute myocardial infarction.

Patients and Methods

In 1984 69 patients admitted to the coronary care unit with chest pain and suspected acute myocardial infarction were considered for the study (9). Eighteen were excluded (most of them had taken aspirin) leaving 51 patients to be studied. The bleeding time, platelet count and platelet volume distribution were measured within 24 hours after onset of symptoms. Twenty-eight were diagnosed as definite acute myocardial infarction according to the WHO criteria (10, 11). The bleeding time was significantly shorter in the patients with definite acute myocardial infarction (mean = 170 s) than in the 23 controls (mean = 258 s).

Two years later the 51 patients were asked to participate in a follow-up study. The study was approved by the ethics committee. The patients were not allowed to take aspirin or non-steroidal antiinflammatory drugs for 10 days prior to the study or to smoke for 6 hours prior to the study. The techniques used for measuring the bleeding time, platelet count and platelet volume distribution were the same as in 1984. Briefly, the bleeding time was measured after 15 minutes supine rest using the Simplate II device (General Diagnostics, New Jersey, USA) according to the recommendations given by Mielke (12). All measurements were done by the same investigator, who had not performed the bleeding time in 1984 and who was blinded as to the results of these tests. Blood samples were obtained from the cubital vein of the contralateral arm immediately after measurement of the bleeding time. Blood was anticoagulated with sodium citrate/prostaglandin E_1. The platelet volume distribution was measured by a resistive particle counter coupled to a computer via an analogue-to-digital converter in a representative population of platelets separated from whole blood by velocity sedimentation in continuous non-linear Percoll gradients (13). Platelet recovery was calculated as the ratio between the platelet count in the platelets obtained from the gradient and the platelet count in whole blood. The relative frequencies of small platelets (<6 fl), medium-sized (6 to 13 fl) and large platelets (>13 fl) were obtained from the platelet volume distribution curve using a computer program.

The patients were interviewed and their smoking habits and medical treatment were recorded. Possible acute myocardial infarctions since 1984 were recorded and classified according to the WHO criteria. Numbers of deaths were registered. In the control group the diagnosis "ischaemic heart disease" was made according to the clinical history at the time of study and at earlier admissions and subsequently adjusted in the light of new findings.

Differences between the 1984 and 1986 values of the bleeding time, platelet count and platelet recovery were assessed using the Wilcoxon matched pair signed rank test. The relative frequencies of platelets in the 3 volume subgroups at the 2 occasions were compared using the sign test. Differences in the 1986 values between myocardial infarction patients and the controls were assessed using the Mann-Whitney U test. In the myocardial infarction group the 1984 values of the patients who died were compared to the ones that survived using the Mann-Whitney U test. The mean platelet volume was calculated from the platelet volume distribution and was used for correlation studies. All correlations were by the Spearman rank method. All probabilities were based on two tailed tests. Results were expressed as median values with interquartile intervals in brackets.

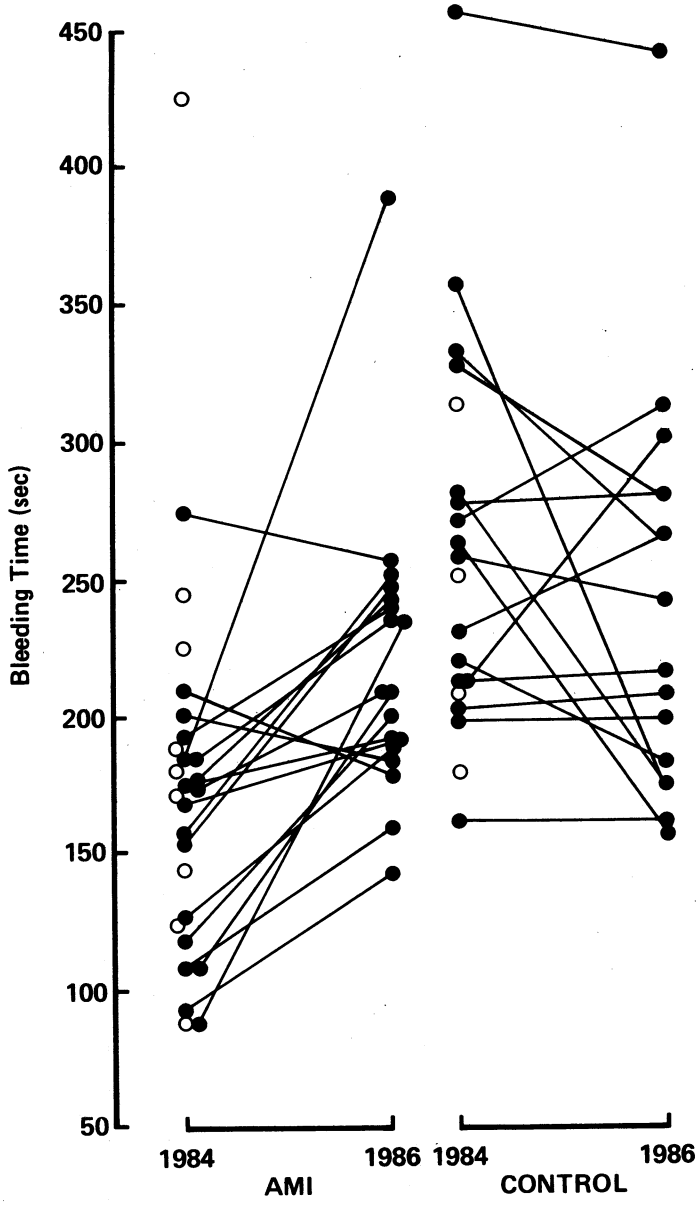

Fig. 1 Bleeding times (sec) in 18 patients with definite acute myocardial infarction (AMI) and in 16 patients admitted with chest pain but no definite myocardial infarction (CONTROL) at the time of admission (1984) and at the time of follow-up (1986). The bleeding time was significantly prolonged in the AMI group at the time of follow-up compared to the values obtained during the acute myocardial infarction ($p < 0.01$). O indicate values for the patients who died

Results

Of the 51 patients considered for the study 13 had died (9 from the myocardial infarction group and 4 controls), 3 patients did not respond to our letters or enquiries (1 myocardial infarction, 2 controls) and one patient (control) was undergoing treatment with naproxen leaving 18 patients with definite myocardial infarction and 16 controls in the two groups. Three of the patients participating in the follow up study had suffered from a new acute myocardial infarction since 1984 (2 myocardial infarction, 1 control). One patient (control) had had coronary by-pass surgery. Nine of the control patients had ischaemic heart disease. In one of these patients we were unable to obtain a suitable blood sample. None of the patients had been admitted to hospital during the 6 weeks prior to the study. Median ages of the myocardial infarction group and the control group were 60 years (range 51–74 years) and 58 years (range 36–69 years) respectively. There were 2 women in the myocardial infarction group and 6 in the control group. The platelet recoveries in the patients with definite myocardial infarction were 93% (90%–97%) at the time of infarction and 94% (91%–96%) at the time of follow-up. In the control group the values were 92% (90%–96%) at the time of admission and 92% (90%–97%) 2 years later. No statistically significant differences in platelet recovery could be demonstrated between the two groups or within the two groups at the time of admission and at the time of follow-up.

In the myocardial infarction group the bleeding time was significantly prolonged now (209 s [190–245 s]) compared to the value obtained during the infarction (162 s [120–186 s]) ($p < 0.01$, Figure 1). In the control group the bleeding time was shorter 2 years later (228 s [207–285 s]) than at the time of admission (258 s [215–282 s]) (Figure 1), but this decrease was not statistically significant.

In the myocardial infarction group comparison of the relative frequencies of platelets in the 3 volume subgroups (Table 1) showed that in 15 of the 18 patients the percentage of small platelets was higher ($p < 0.01$), in 16 of the 18 patients the percentage of medium-sized platelets was lower ($p < 0.01$) and in 14 of the 18 patients the percentage of large platelets was lower ($p < 0.05$) at the time of acute myocardial infarction that at the time of follow-up. In the control group there was no statistically significant changes in any of the platelet volume subgroups at the 2 occassions. No statistically significant changes in platelet count could be demonstrated in the myocardial infarction group (1984: 240×10^9/l [188×10^9/l–10^9/l]; 1986: 246×10^9/l [193×10^9/l–314×10^9/l]) or in the control group (1984: 230×10^9/l [156×10^9/l–264×10^9/l]; 1986: 225×10^9/l [187×10^9/l–266×10^9/l]).

At the time of follow-up there were no statistically significant differences in bleeding time or platelet count between the myocardial infarction and the control group. When considering the values obtained in 1984 none of these variables were statistically significantly different when comparing the group of patients with myocardial infarction that died to the group with myocardial infarction that survived. In the myocardial infarction group the number of patients that received medical treatment for angina had increased from 4 to 8 since 1984. Two of the myocardial infarction patients had stopped smoking. The changes in medication and smoking habits were not related to changes in the bleeding time or platelet variables.

In the patients with ischaemic heart disease ($n = 26$) the bleeding time was found to be negatively correlated to mean platelet volume ($r_s = 0.44$, $p < 0.03$). No correlation between bleeding time and platelet count could be demonstrated in either the group with ischaemic heart disease or when considering all cases.

Discussion

The shortened bleeding time occurring during an acute myocardial infarction (9) indicates an increased reactivity of platelets and/or an enhanced interaction of the platelets with the vessel wall. This finding is of potential clinical importance. Even though it remains unknown whether the change in bleeding time preceeds the myocardial infarction or is an acute change secondary to the infarction, the fact that it is considerably shorter implies systemic haemostatic and/or vascular changes chronologically associated with myocardial infarction. If these changes are not related to the cause of the infarction, they may be associated with the lack of dissolution of the coronary artery clot or

Table 1 The relative frequencies of small (<6 fl), medium-sized (6–13 fl) and large (>13 fl) platelets in 18 patients at the time of definite acute myocardial infarction (1984) and at the time of follow-up (1986). Δ% indicates the absolute difference between 1984 and 1986 values for each volume subgroup

1984			1986					
<6 fl	6–13 fl	>13 fl	<6 fl	6–13 fl	>13 fl	<6 fl Δ%	6–13 fl Δ%	>13 fl Δ%
44.1%	46.5%	9.4%	37.1%	50.2%	12.7%	− 7.0%	+ 3.7%	+3.3%
47.2%	44.9%	7.9%	47.6%	45.2%	7.2%	+ 0.4%	+ 0.3%	−0.7%
42.7%	47.9%	9.4%	35.3%	53.4%	11.3%	− 7.4%	+ 5.5%	+1.9%
55.0%	40.1%	4.9%	53.4%	41.4%	5.2%	− 1.6%	+ 1.3%	+0.3%
42.8%	48.2%	9.0%	35.8%	52.5%	11.7%	− 7.0%	+ 4.3%	+2.7%
34.6%	52.8%	12.6%	34.5%	53.6%	11.9%	− 0.1%	+ 0.8%	−0.7%
43.8%	47.9%	8.3%	38.7%	50.4%	10.9%	− 5.1%	+ 2.5%	+2.6%
41.2%	48.9%	9.9%	35.3%	53.1%	11.6%	− 5.9%	+ 4.2%	+1.7%
54.9%	40.5%	4.6%	58.8%	37.3%	3.9%	+ 3.9%	− 3.2%	−0.7%
48.2%	45.0%	6.8%	44.8%	47.2%	8.0%	− 3.4%	+ 2.2%	+1.2%
42.8%	49.3%	7.9%	36.8%	53.7%	9.5%	− 6.0%	+ 4.4%	+1.6%
48.1%	44.2%	7.7%	31.7%	53.2%	15.1%	−16.4%	+ 9.0%	+7.4%
54.6%	40.9%	4.5%	50.9%	43.9%	5.2%	− 3.7%	+ 3.0%	+0.7%
60.0%	36.0%	4.0%	48.3%	46.0%	5.7%	−11.7%	+10.0%	+1.7%
50.2%	42.3%	7.5%	46.3%	44.5%	9.2%	− 3.9%	+ 2.2%	+1.7%
58.0%	37.2%	4.8%	51.2%	42.9%	5.9%	− 6.8%	+ 5.7%	+1.1%
59.1%	37.6%	3.3%	54.0%	41.6%	4.4%	− 5.1%	+ 4.0%	+1.1%
48.4%	44.5%	7.1%	49.0%	44.4%	6.6%	+ 0.6%	− 0.1%	−0.5%

intramyocardial or systemic thrombotic events closely following the immediate event of infarction.

The results of the present study show that the reported shortened bleeding time during the first 24 hours of an acute myocardial infarction (9) is associated with the acute event itself. Two years later the bleeding time had lengthened significantly in the myocardial infarction group and was no longer different from the bleeding time of an age matched control group in which more than half the patients had ischaemic heart disease. Although the operator measuring the bleeding time was different in 1984 and now, the prolongation of the bleeding time in the myocardial infarction group is unlikely to be caused by differences in methodology because the bleeding time in the control group was found to be shorter at time of follow-up. No difference in the bleeding time measured at the time of the infarction between the patients who died or the ones that survived could be demonstrated, thus arguing against the possibility that the change in bleeding time in the myocardial infarction patients could be explained by a selection of patients with a longer bleeding time. The bleeding time values found in patients with ischaemic heart disease in the present study are of the same order of magnitude as the values reported by Jørgensen et al. (14) in healthy persons of a similar age.

The negative association between bleeding time and mean platelet volume demonstrated here suggests that the evidence, derived from studies on animals (15), healthy humans (4) and patients with thrombocytopenia (3), that large platelets are more haemostatically active, also is valid in patients with ischaemic heart disease. However, large platelets are unlikely to be directly responsible for the shortened bleeding time in the acute phase of myocardial infarction, because at the time of follow-up there were more large and medium-sized platelets present whereas the bleeding time was lengthened. These findings suggest that other major unknown factors are responsible for the shortened bleeding time in acute myocardial infarction. Substances like thromboxane A_2 or catecholamines that can cause increased platelet reactivity and vasoconstriction might be involved. Catecholamine levels in plasma are increased during the first 24 hours of acute myocardial infarction (16). However, our control group were also suffering from chest pain and were in the same external environment as the patients. Increased thromboxane A_2 concentrations have been claimed to be of pathogenetic importance in acute myocardial infarction (17, 18, 19). Platelet size is increased in acute myocardial infarction (5, 6, 20) and subpopulations of large platelets isolated from healthy humans have been shown to produce more thromboxane B_2 in response to stimulation with collagen or thrombin than small platelets from the same individuals (21). Furthermore, increased concentrations of thromboxane B_2 has been found in blood emerging from skin incisions in men with a short bleeding time (22). Indirect evidence that thromboxane A_2 is important for the development of acute myocardial ischaemia comes from the multicentre trials showing beneficial effect of aspirin in unstable angina pectoris (23, 24).

The mean platelet volume is larger in patients during the acute phase of a myocardial infarction compared to a group of healthy controls (5, 6) or to patients with chest pain (20). Our finding that relatively more small and fewer medium-sized and large platelets are present at the time of infarction compared to 2 years later is in disagreement with the results of Sewell et al. (7), who found relatively fewer small platelets to be present at the time of infarction. The reason for this discrepancy could be due to the differences in design and methodology in the 2 studies. In the study published by Sewell et al. (7) the patients used as controls were poorly defined and the control groups were different at the time of the first study and at the time of follow up. Our control group was well defined by WHO criteria and the same patients were used on the 2 occasions. Sewell et al. (7) used potassium EDTA as anticoagulant which has been shown to cause a time dependent increase in platelet volume (25, 26), whereas the citrate/PGE_1 used here is without effect on platelet volume (26).

The platelet count is lower in patients suffering from an acute myocardial infarction than in patients with ischaemic heart disease admitted with chest pain (20, 27). The platelet count decreases during the first four days after the infarction and the magnitude of this decrease is related to the size of the infarction (28). Also in the present study the platelet count was lower at the time of acute myocardial infarction than at the time of follow-up. However, this difference was not statistically significant. Since large platelets have been shown to be consumed during severe traumatic bleeding episodes (29), our present finding of a deficiency of medium-sized and large platelets in venous blood during acute myocardial infarction could be interpreted in terms

of consumption of these large reactive platelets at the time of thrombus formation or alternatively in terms of transient selective sequestration of large platelets in the spleen (30, 31). If so the mean platelet volume before the initiation of thrombus formation would have been even larger and these large platelets could be important in the development of acute myocardial infarction.

Platelets are produced from megakaryocytes and platelet size and density are determined at time of thrombopoiesis (13, 32, 33, 34). In patients suffering from acute myocardial infarction or sudden cardiac death megakaryocyte size is increased (35). In an animal model such large megakaryocytes produced platelets which disproportionally decreased the bleeding time and produced more thromboxane B_2 per unit volume of platelet cytoplasm compared with platelets produced from megakaryocytes of normal size (15). Also in experimental atherosclerosis the vascular changes are associated with an increase in megakaryocyte size and ploidy (36). It seems likely that changes occuring in the megakaryocytes are important for the development of vascular disease and its complications, and further studies are needed to evaluate the relation between megakaryocyte and haemostatic variables and to investigate megakaryocyte variables in ischaemic heart disease. The variable that causes bleeding time changes at the time of infarction still remains to be determined.

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