

Depressed Platelet Status in an Elderly Patient With Hemorrhagic Stroke After Thrombolysis for Acute Myocardial Infarction

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Background—Impaired platelet function has been reported in acute myocardial infarction (AMI) and stroke. However, prospective data on the changes of platelet status in patients before the occurrence of hemorrhagic stroke after thrombolytic therapy are unavailable.

Case Description—An 86-year-old male patient was among the 23 AMI patients enrolled in the platelet study for the GUSTO-III trial. He received 325 mg of aspirin daily for at least 6 years, suffered an AMI, and was successfully reperfused with alteplase, but after 44 hours developed a large hemorrhagic stroke resulting in paraplegia. Platelet aggregation and receptor expression were measured by flow cytometry and ELISA before thrombolysis and at 3, 6, 12, and 24 hours thereafter. The percentage of platelet aggregation was lower in the stroke patient at every time point when induced by 5 μ mol/L of ADP, by 10 μ mol/L of ADP, and by thrombin than in the rest of the AMI group. Ristocetin and collagen-induced aggregability were within the group range. Decreased platelet glycoprotein Ib, IIb, IIIa, and IIb/IIIa and vitronectin receptor expression were observed in the stroke patient. No other differences in p24 (CD9), very late antigen-2, P-selectin, and platelet/endothelial cell adhesion molecule-1 expression were determined.

Conclusions—Profound depression of platelet status preceded the occurrence of hemorrhagic stroke in an elderly long-term aspirin user treated with thrombolytic therapy. Initial “exhausted” platelets may be responsible for the increased risk for hemorrhagic stroke after coronary thrombolysis. (*Stroke*. 1998;29:235-238.)

Key Words: hemorrhagic stroke ■ myocardial infarction ■ platelets ■ thrombolysis

Platelets have been implicated as important components in the natural history of acute myocardial infarction (AMI)¹ and stroke.² Thrombolytic agents remain the cornerstone of treatment for patients with AMI, whereas intracerebral bleeding is the most serious complication of their use.^{3,4} There is substantial evidence from in vitro⁵⁻⁷ and animal studies^{8,9} that impaired platelet function occurs after thrombolytic therapy and may play a role in the occurrence of intracranial hemorrhage. However, prospective dynamic data on the platelet status in patients before the occurrence of hemorrhagic stroke after thrombolytic therapy for AMI are unavailable.

We describe an elderly patient with an AMI who was enrolled in the GUSTO-III trial and underwent serial measurements of platelet aggregability, soluble receptor levels, and major surface receptor expression who later developed an intracerebral hemorrhage.

Case Report

An 86-year-old man with no prior cardiac history was admitted to the emergency department of St Agnes Hospital with

2.5 hours of left arm pain and chest discomfort. Blood pressure was 129/75 mm Hg, and pulse was 85 beats per minute. The physical examination was unremarkable. Past medical history was relevant for a hemicolectomy for villous adenoma. There was no history of bleeding diathesis or tobacco or alcohol use. The patient had received 325 mg of aspirin daily for the last 6 years. There were no other concomitant medications. The electrocardiogram demonstrated normal sinus rhythm with Q waves in leads V₁ through V₃ and ST segment elevation in leads V₁ through V₄, indicating an acute anteroseptal myocardial infarction. The white blood cell count was 8400/mL, platelet count was 196 000/mL, and the hematocrit was 44.5%. The blood urea nitrogen was 14 mg/dL, and creatinine was 1.1 mg/dL. The activated partial thromboplastin time was 34 seconds. The prothrombin time was 14 seconds.

The patient was treated with 325 mg of aspirin and 5000 U of intravenous heparin, followed by a continuous infusion of heparin as recommended in the GUSTO-III protocol. The patient was randomized to treatment with 100 mg of alteplase (15 mg bolus followed by 85 mg infusion over 90 minutes).

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Selected Abbreviations and Acronyms

AMI = acute myocardial infarction

Chest pain resolved within the first hour, and there was no evidence of congestive heart failure or arrhythmia. The peak creatine kinase (CK) was 554 IU/L, and peak CK-MB was 51 IU/L. Heparin was discontinued after 24 hours. At 36 hours, the activated partial thromboplastin time was 40 seconds, and the platelet count was 211 000/mL.

Approximately 44 hours after admission, the patient developed progressive confusion and left hemiplegia. A computed tomographic scan of the head demonstrated at least three areas of focal intracerebral hemorrhage. In light of these findings, aspirin was discontinued. An echocardiogram demonstrated anteroseptal hypokinesis and ejection fraction estimated at 40% to 45%, with no significant valvular heart disease. No embolic foci were identified. The neurological status improved after a prolonged hospitalization, and the patient was transferred to a subacute facility for further rehabilitation.

Blood samples were obtained before thrombolysis and at 3, 6, 12, and 24 hours thereafter. The table summarizes the baseline platelet aggregability in response to different agonists, flow cytometry of platelet surface receptors, and ELISA measurements of soluble antigens in the described patient compared with the rest of the AMI group and healthy control subjects.

Platelet characteristics were severely depressed in this patient compared with control subjects and the AMI group. Platelet aggregation in response to ADP (both 5 and 10 μ mol/L) and thrombin were the lowest among the AMI patients. Collagen- and ristocetin-induced platelet aggregability were diminished, but within the group range. The lowest surface receptor expression among the AMI group was observed for platelet glycoproteins Ib (\downarrow 64%), IIb (\downarrow 25%), IIIa (\downarrow 39%), IIb/IIIa (\downarrow 72%), and the vitronectin receptor (\downarrow 55%). The patient with intracerebral hemorrhage also had lower levels of soluble substances indicative of platelet activation (P-selectin and platelet-endothelial cell adhesion molecule [PECAM]-1) before thrombolysis. Compared with baseline, we observed some changes of the platelet status after thrombolytic therapy. The patterns of these changes were similar in the patient with the hemorrhagic stroke compared with the rest of AMI group. Early in thrombolysis (3 to 6 hours), we observed minor reductions of platelet aggregation and receptor expression together with a substantial increase of soluble P-selectin and PECAM-1 plasma concentrations. Later in thrombolysis (12 to 24 hours), we found a slight elevation of platelet aggregability, an increase in specific expression of glycoprotein IIb/IIIa, very late antigen-2, and PECAM-1 with no further changes of soluble P-selectin and PECAM-1. The dynamics of these receptors over 24 hours are shown in the figure.

Baseline Platelet Status in Patient With Stroke Compared With the Rest of AMI Population and Healthy Controls*

Parameter	Control Subjects (n=10)	AMI Patients (n=22)	Patients With Stroke
Aggregation, %			
1. ADP 5 μ mol/L	52.0 \pm 6.7 (39-61)	66.3 \pm 11.4 (47-82)	42
2. ADP 10 μ mol/L	59.2 \pm 7.2 (45-67)	73.8 \pm 12.0 (54-90)	49
3. Collagen 1 mg/mL	66.2 \pm 5.9 (58-74)	64.7 \pm 6.9 (49-72)	66
4. Thrombin 1 mg/mL	60.5 \pm 6.9 (49-71)	75.8 \pm 10.9 (59-94)	54
5. Ristocetin 1.25 mg/mL	71.3 \pm 7.4 (59-84)	92.5 \pm 7.8 (72-100)	84
Surface Receptor Expression, log fluorescence			
1. CD9 (ρ 24)	41.07 \pm 11.40 (20.37-58.11)	55.12 \pm 17.23 (18.12-79.04)	51.44
2. GP Ib	133.76 \pm 7.96 (124.43-148.21)	103.62 \pm 29.89 (39.28-161.02)	37.18
3. GP IIb	37.19 \pm 1.73 (34.28-40.03)	28.42 \pm 2.52 (24.44-33.21)	22.76
4. GP IIIa	320.29 \pm 25.20 (278.90-361.00)	326.97 \pm 51.78 (211.56-418.22)	201.06
5. GP IIb/IIIa	53.02 \pm 6.95 (40.29-61.27)	59.24 \pm 16.3 (18.12-79.04)	16.39
6. VLA-2	41.36 \pm 2.14 (38.78-45.13)	40.18 \pm 4.66 (33.03-51.19)	45.18
7. P-Selectin	25.11 \pm 2.56 (20.67-29.95)	31.54 \pm 4.96 (22.18-40.04)	27.90
8. PECAM-1	44.47 \pm 3.75 (38.18-49.14)	56.84 \pm 17.69 (26.28-81.07)	61.12
9. Vitronectin	59.76 \pm 6.00 (44.96-65.05)	60.16 \pm 25.56 (29.24-129.40)	27.15
Soluble Receptors, ng/mL			
1. P-selectin	10.24 \pm 1.07 (9.06-11.60)	26.13 \pm 12.93 (10.35-57.24)	9.82
2. PECAM-1	27.74 \pm 6.49 (20.29-36.80)	35.19 \pm 9.66 (18.55-48.19)	19.20

AMI indicates acute myocardial infarction; GP, glycoprotein; VLA, very late antigen; and PECAM, platelet-endothelial cell adhesion molecule.

*Results are expressed as mean \pm SD. Ranges are given in parentheses.

Fig. 1A

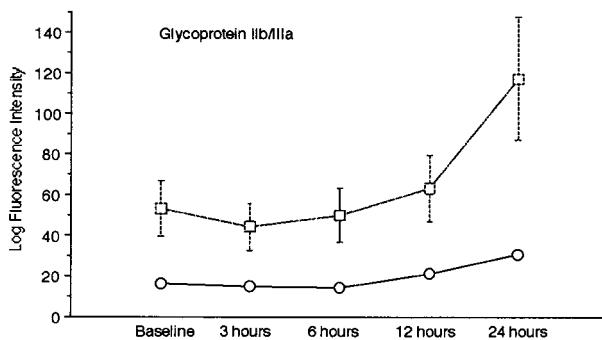


Fig. 1B

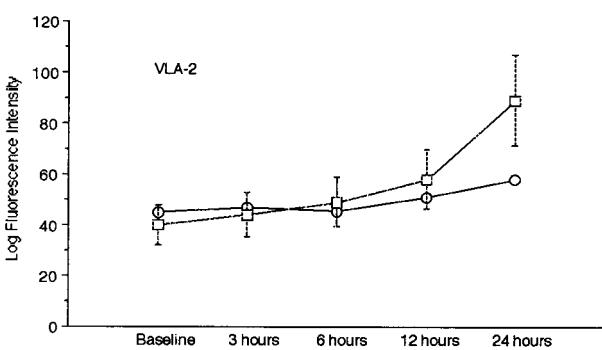
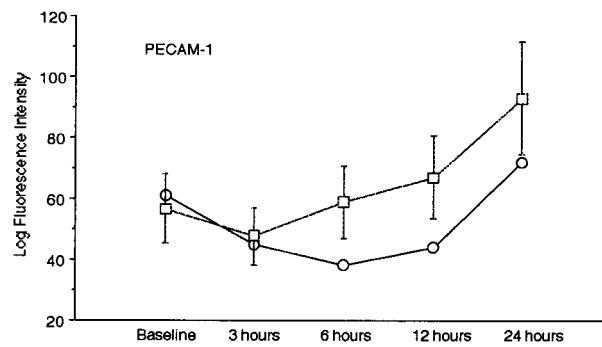


Fig. 1C



Dynamic changes of the glycoprotein IIb/IIIa expression (A), very late antigen (VLA)-2 (B), and platelet-endothelial cell adhesion molecule (PECAM)-1 (C) during the first 24 hours after thrombolysis. ○ represents patient with future stroke; □ represents the rest of the AMI population.

Discussion

The present report emphasizes the potential importance of baseline platelet characteristics in the pathogenesis of hemorrhagic stroke after thrombolytic therapy for AMI. We attempted to correlate antecedent platelet status by using conventional aggregometry, ELISA, and flow cytometry techniques, with an episode of hemorrhagic stroke in the oldest patient enrolled in the GUSTO-III platelet study.

The major complication of thrombolytic therapy is hemorrhagic stroke, which occurs in 1.2% to 1.9% of treated AMI patients.¹⁰⁻¹² Platelets have been implicated in both ischemic^{13,14} and hemorrhagic^{15,16} stroke. However, all of these studies have been performed in the relatively late phases of acute stroke and could be confounded by the natural history of the disease and the effects of various concomitant medications. The prospective assessment of the platelet status in the con-

trolled clinical trial provides us with a unique opportunity to characterize the patient's platelets before the occurrence of stroke.

It should be noted that none of the measured platelet aggregation agonists, soluble antigens, or surface receptors served as a specific marker exclusively affected in the described patient. In contrast, we found a profound depression of multiple platelet-related characteristics. This finding leads us to an important observation. We can no longer hypothetically assume that platelets are necessarily systemically activated during the initial pre-reperfusion phase of AMI.

Another meaningful issue is the long-term use of relatively high doses of aspirin, which was documented in the described patient. However, there is no evidence that depressed platelet characteristics in this patient were directly related to the antecedent aspirin therapy.

This preliminary report also suggests that the adequate and timely assessment of platelet activity may be critical in assessing the risk for hemorrhagic stroke. Bleeding events after standard thrombolytic and/or antiplatelet therapy could be related to the decreased platelet characteristics in such patients. It is not clear whether we should uniformly use aggressive thrombolytic strategies without individual assessment of platelet status in AMI patients. Based on the present case, it is reasonable to speculate that the early bleeding complication observed after modern therapy could be, at least in part, related to depressed baseline platelet characteristics.

In conclusion, the ability to define patients at risk of hemorrhagic stroke after thrombolysis in AMI cannot be overstated. If platelets indeed are vital elements of the acute coronary and cerebrovascular events, then their characteristics could affect the response to thrombolytic therapy and clinical outcome. In our case, profound depression of platelet status preceded the occurrence of hemorrhagic stroke in an elderly patient who was successfully reperfused. Dysfunctional platelets may be responsible for the increased risk of provoking hemorrhagic stroke after thrombolysis. Further analysis of the baseline platelet status and its clinical significance during acute vascular syndromes remains to be determined.

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References

1. Becker RC, Bovill EG, Corrino JM, Ball SP, Ault K, Mann K, Tracy RP. Platelet activation determined by flow cytometry persists despite anti-thrombotic therapy in patients with unstable angina and non-Q-wave myocardial infarction. *J Thromb Thrombolys*. 1994;1:95-100.
2. Shah AB, Beamer N, Coull BM. Enhanced in vivo platelet activation in subtypes of ischaemic stroke. *Stroke*. 1985;16:643-647.
3. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673-682.
4. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *Lancet*. 1990; 336:71-75.

5. Cronberg S. Effect of fibrinolysis on adhesion and aggregation of human platelets. *Thromb Diath Haemorrh*. 1968;19:474-482.
6. Terres W, Unmus S, Mathey DG, Bleifeld W. Effects of streptokinase, urokinase, and tissue plasminogen activator on platelet aggregability and stability of platelet aggregates. *Cardiovasc Res*. 1990;67:1175-1181.
7. Torr SR, Winters KJ, Santoro SA, Sobel BE. The nature of interactions between tissue-type plasminogen activators and platelets. *Thromb Res*. 1990;59:279-293.
8. Golino P, Ashton JH, Glas-Greenwalt P, McNatt J, Buja LM, Willerson JT. Mediation of reocclusion by thromboxane with tissue type plasminogen activator in a canine preparation of coronary thrombosis. *Circulation*. 1988;77:678-684.
9. Nicolini FA, Lee P, Rios G, Kottke-Merchant K, Topol EJ. Combination of platelet fibrinogen receptor antagonist and direct thrombin inhibitor at low doses markedly improves thrombolysis. *Circulation*. 1994;89:1802-1809.
10. Gurbel PA, Navetta FI, Bates ER, Muller DW, Tenaglia AN, Miller MJ, Muhlstein B, Hermiller JB, Davidson CJ, Aguirre FV, Beauman GJ, Berdan LG, Leimberger JD, Bovill EG, Christenson RH, Ohman EM. Lesion-directed administration of tissue plasminogen activator with intracoronary heparin in patients with unstable angina and coronary thrombus undergoing angioplasty. *Cathet Cardiovasc Diagn*. 1996;37:382-391.
11. O'Connor CM, Meese RB, McNulty S, Lucas KD, Carney RJ, LeBoeuf RM, Maddox W, Bethea CF, Shadoff N, Trahey TF, Heinheimer JA, Burks JM, O'Donnell G, Krucoff MW, Califf RM, the DUCCS-II Investigators. A randomized factorial trial of reperfusion strategies and aspirin dosing in acute myocardial infarction. *Am J Cardiol*. 1996;77:791-797.
12. Smalling RW, Bode C, Kalbfleisch J, Sen S, Limbourg P, Forycki F, Habib G, Feldman R, Hohnloser S, Seals A, RAPID Investigators. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation*. 1995;91:2725-2732.
13. Uchiyama S, Yamazaki M, Maruyama S, Handa M, Ikeda Y, Fukuyama M, Itagaki I. Shear-induced platelet aggregation in cerebral ischemia. *Stroke*. 1994;25:1547-1551.
14. Toghi H, Suzuki H, Tamura K, Kimura B. Platelet volume, aggregation and adenosine triphosphate release in cerebral thrombosis. *Stroke*. 1991;22:17-21.
15. Sobel BE. Intracranial bleeding, fibrinolysis, and anticoagulation: causal connections and clinical implications. *Circulation*. 1994;90:2147-2152.
16. Olson JD. Mechanisms of hemostasis: effect on intracerebral hemorrhage. *Stroke*. 1993;24(suppl 12):109-114.

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