Letters to the Editor

Morbidity of Intracranial Hemorrhage in Patients With Cerebral Arteriovenous Malformation

To the Editor:

The Columbia-Presbyterian Medical Center Arteriovenous Malformation Study Project has made, and continues to make, a significant contribution to our understanding of arteriovenous malformations of the brain. In the recent contribution of Hartmann et al.,1 a number of interesting observations were made with regard to hemorrhage. The first is the high incidence among those that bleed of subarachnoid and intraventricular hemorrhage. Only 54% of initial hemorrhages and 49% of follow-up hemorrhage were intraparenchymal. This is at considerable variance with our experience at the Northern and Western Medical School, The University of Sydney, where we have followed all arteriovenous malformations (AVMs) seen since 1991, and of 114 patients presenting with hemorrhage, 82% have a significant intraparenchymal component.

One is left with the feeling from this article that hemorrhage from AVMs is relatively benign. However, it must be borne in mind that this is a specially selected subset of patients referred to a tertiary service. The authors of this article acknowledge that they were not able to ascertain the number of patients that were ineligible for referral because of death. One also wonders whether patients with a poor quality of life as a result of hemorrhage, the likelihood is that this second hemorrhage is also a significant intraparenchymal component.

A most interesting aspect of the article is the relatively benign second hemorrhage experienced by 27 patients. As with the initial hemorrhage, many of these cases appear to have been nonparenchymal hemorrhage. Although too much should be made of such small numbers, it does raise the prospect that in those patients for whom the first hemorrhage was benign, a second hemorrhage experienced within 4 years of the first is also relatively benign. This should not be a surprise given that the pathophysiology of an AVM may not have been much changed by an initial benign hemorrhage; therefore, the force of a subsequent hemorrhage may well be similar to that of the first hemorrhage. Although we have seen patients with a subsequent hemorrhage die, we have also a small group of patients in whom repeat hemorrhages were a clinical copy of their initial hemorrhage. However, we have been concerned that the hemodynamics may change with time, and more temporally distant subsequent hemorrhages may be less likely to mimic the initial hemorrhage. This may explain the devastating consequences of harboring an AVM in the study reported by Ondra et al.,3 in which 85% of 64 patients sustaining a hemorrhage after study enrollment died or suffered major permanent morbidity. The mean follow-up of this study was 24 years.

Therefore, we suggest that if these findings are confirmed with larger numbers, one should conclude that for those who experience a second hemorrhage shortly after an initial benign hemorrhage, the likelihood is that this second hemorrhage is also benign. No statement can be made regarding the initial hemorrhage or remote subsequent hemorrhage.

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Response

We thank Drs Morgan et al for their thoughtful comments. They represent a group that has contributed substantially to the study of brain AVM.

Regarding the issue of possible referral biases to tertiary centers such as ours, we recently presented data from 1266 patients from several AVM databases (Berlin, New York, Paris, Toronto).1 The results suggest that our sample may be representative in many major clinical and morphological aspects. Also, we offer the opinion that the important contributions of other authors, cited by Morgan et al and discussed in our article, may be influenced by the retrospective nature of the observations and the selection of patients deemed untreatable. Our study is the first to date providing prospective data for patients that survived their diagnostic event. Given the current therapeutic options and the higher risk of further hemorrhage for patients presenting with a bleed,2 long-term follow-up studies in unselected untreated samples as proposed by Morgan et al will be difficult to conduct because of the strong desire for interventional treatment of a potentially life-threatening disease.

We agree, and so stated in the article, that the paucity of natural history data remains a major concern, especially in that serious hemorrhages may be underrepresented in case series from referral centers. To address these concerns, we have proposed a prospective population-based study (http://cpmcnet.columbia.edu/dept/avm).

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

To the Editor:

I read with great interest the above-titled article by Serebruany and colleagues.1 This report is special because prospective data are available regarding the changes of platelet functions before the occurrence of hemorrhagic stroke following thrombolysis.1 I would like to make the following comments and report the case of an elderly Chinese man who developed a cerebellar hematoma after thrombolysis for acute myocardial infarction (MI) when thrombocytopenia was induced by low-molecular-weight heparin.

First, hemorrhagic stroke is a major complication of thrombolysis for acute MI, even though patients with a recent history of stroke were excluded from clinical trials on thrombolysis in acute MI.2,3 In general, hemorrhagic stroke after thrombolysis in acute MI occurs within the first 24 to 48 hours of treatment; the hematoma is commonly lobar in location and occasionally multifocal; and the risk of hemorrhagic stroke is greater with tissue plasminogen activator than streptokinase.2,3 I wonder whether the index patient of Serebruany et al1 had a history of recent transient ischemic attack or a history of stroke longer than 6 months. I also wonder whether his arterial blood pressure was high when he was treated with tissue plasminogen activator. The platelet count was normal, but the activated partial thromboplastin time was mildly prolonged at 36 hours after thrombolysis,1 and I am interested in knowing about any disturbance in his coagulation and/or platelet count immediately after the development of neurological symptoms at 44 hours.

Second, I have two concerns when reviewing the comprehensive platelet function tests. Although many platelet functions of the index patient were rather “abnormal” compared with the mean results of the group of patients with acute MI and those of the control group, the absolute results were either within or very close to the lower limit of the “normal” range provided by the two groups of subjects (see the Table1). It would be interesting to speculate why hemorrhagic stroke did not occur in the other patients and control subjects whose results were more abnormal than those of the index patient in some platelet function tests. In addition, the platelet functions appeared to improve spontaneously in all patients, including the index patient, after thrombolysis. Nevertheless, the hemorrhagic stroke occurred at 44 hours after thrombolysis in the index patient, when his platelet functions were improving (see the Figure1). While it is unfortunate that the results of platelet function tests at a later time were unavailable, I wonder whether the authors can explain the timing of hemorrhagic stroke in relation to the changes in platelet functions of the index patient.

Finally, I would like to briefly describe a 76-year-old Hong Kong Chinese man whose depressed platelet count contributed to the occurrence of hemorrhagic stroke after thrombolysis for acute MI. This patient, who had no history of stroke or transient ischemic attack, presented initially with chest pain and ECG changes indicating acute inferior MI. Streptokinase (1.5 million U IV) was given over a 1-hour period, and his chest pain subsided, together with complete resolution of the ECG changes. Subsequently, he was given subcutaneous low-molecular-weight heparin and oral aspirin (300 mg loading dose followed by 150 mg daily). Serial cardiac enzymes confirmed acute MI. Forty-six hours after his first MI, his chest pain recurred with ECG changes of acute anterior MI. A second dose of streptokinase was given, and once again his chest pain subsided, together with complete resolution of the ECG changes. Ten hours after the second dose of streptokinase, he awoke with a headache, confusion, and dizziness. Urgent CT of his brain revealed a right cerebellar hematoma 2.5 cm in diameter; blood tests revealed coagulopathy and thrombocytopenia, and his platelet count was reduced to 89,000/mL. His arterial blood pressure remained stable throughout the admission. The cerebellar hematoma was managed conservatively, together with cessation of low-molecular-weight heparin and aspirin and transfusion of fresh frozen plasma and platelet concentrate. He was discharged without neurological deficit, and his latest platelet count was 269,000/mL. The thrombocytopenia was probably induced by treatment with low-molecular-weight heparin, and the antiplatelet antibody was negative. I wonder whether the authors have encountered thrombocytopenia following thrombolysis and use of heparin in patients with acute MI.

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Response

We thank Dr Cheung for his interest and comments regarding our GUSTO-III case report.1 Indeed, they are the only prospective data available that support the concept of platelet hypofunction as a risk factor for intracranial hemorrhage after systemic thrombolysis for MI. Dr Cheung correctly points out that known cerebrovascular disease and systemic hypertension are risk factors for intracranial hemorrhage following thrombolytic therapy with any agent. Neither of these risk factors was present in our patient. Coagulopathy, either induced or spontaneous, also can increase hemorrhagic events but was not observed significantly in the index patient. Moreover, the platelet count in our patient was stable throughout the hospital course.

Dr Cheung also correctly points out that a few of the acute MI patients exhibited slightly higher platelet aggregation than our patient in response to collagen and ristocetin; however, the index patient represented the lowest level in 7 of 14 of receptor expression and function tests. Clearly, there is heterogeneity of platelet activity in acute MI, and not all patients have highly active platelets.2 Our major concern, and the stimulus for this report, involves the uniform dosing regimens of antiplatelet agents in many clinical trials, particularly those involving the elderly, without accounting for the variability of baseline platelet function.

Occurrence of stroke depends on multiple factors.3 Platelet hypofunction may be just one of them. Later after thrombolysis, the pattern of platelet characteristics was similar between the
described patient and the rest of the acute MI group; however, platelet function remained well below the mean. The GUSTO-III platelet study assessed platelets in a prospective manner over the first 24 hours after the start of thrombolysis.\textsuperscript{4} It is possible that the clinical manifestations of the intracranial hemorrhage occurred well after the initial onset of bleeding.

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2. Serebruany VL, Gurbel PA, Shustov AR, Ohman EM, Topol EJ. Heterogeneity of platelet aggregation and major surface receptor expression in patients presenting with acute myocardial infarction. \textit{Am Heart J}. In press.


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