Letters to the Editor

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While the reasons for the differential effect of aspirin in diabetic versus nondiabetic patients remain unclear, it is apparent that there are important subgroup differences in the effect of platelet antiaggregant drugs that are relevant to the use of these drugs in everyday clinical practice. It is critical that future trials of platelet antiaggregant therapy prospectively stratify their patient populations into these relevant subgroups so that enough patients are studied to help clinicians select patients for each therapy. An example of such a trial is the North American Symptomatic Carotid Endarterectomy Trial. Because it stratified patients by severity of carotid stenosis, it is providing clinicians with useful guidelines for selecting patients for surgery. Although subgroup analyses are often maligned as “data dredging,” they are important hypothesis-generating exercises. There are now enough data from the thousands of patients treated with platelet antiaggregant drugs to help identify those risk factors such as diabetes that may affect response to platelet antiaggregant therapy.

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References


Blood Viscosity and Cerebral Blood Flow

In the October 1992 issue of Stroke, Korosue and Heros1 concluded from their findings that in ischemic brain, blood viscosity becomes a major factor determining cerebral blood flow (CBF). We have major doubts that this conclusion can be drawn from their experimental data.

In their ischemic experiments (n=15), they measured CBF “in the presumed area of ischemic penumbra” by hydrogen-sensitive microelectrodes placed into the cortex of rabbits, i.e., in an area in which autoregulatory capacity is impaired or completely exhausted. Ischemia was achieved by a silicone embolus through an internal carotid artery catheter. CBF decreased from 35.2 to 37.2 mL/100 g per minute (cortical flow?) to 14.4±6.4 mL/100 g per minute in five control animals, to 20.1±7.2 mL/100 g per minute in five animals subjected to hemodilution, and to 19.2±6.4 mL/100 g per minute in five animals subjected to hypoxic hypoxia, respectively. The individual CBF values, the individual responses to the decrease of arterial O2 content (aO2Ct), and baseline Paco2 and mean arterial blood pressure (at aO2Ct of 16 mL/DL) were not reported. Moreover, it is difficult to understand why only relative values are given. The relations between CBF and aO2Ct were plotted by using CBF% without defining aO2Ct at 100% CBF. For that reason, one cannot exclude the possibility that some of the electrodes in the hemodilution group measured CBF in a region with preserved perfusion reserve and some did not. Unfortunately, Korosue and Heros did not prove whether resistance vessels were

Is Aspirin Effective in Preventing Strokes in Diabetic Patients?

Sivenius et al2 reported the results of a subgroup analysis of the European Stroke Prevention Study (ESPS) and found that the combination of 900 mg aspirin plus 225 mg dipyridamole daily was much less effective in preventing subsequent stroke in diabetic patients with recent TIA or cerebral infarction than in nondiabetic patients (32% versus 48% risk reduction, respectively). The authors qualify their conclusions by pointing out that only 216 diabetic patients (and only 128 treated with oral drugs or insulin) were randomized into the ESPS and available for on-treatment analysis.

We have recently reported a similar subgroup analysis from the Ticlopidine Aspirin Stroke Study.2 This analysis included a total of 412 diabetic patients who were taking oral hypoglycemic drugs or insulin. Like Sivenius et al, we found that aspirin was much less effective in these diabetic patients, who had a 17% incidence of stroke compared with 10% in nondiabetic patients (p=0.003; Figure 1). The differences were 14% versus 9% in Sivenius’ study. We found no such difference between diabetics not on medication and nondiabetics and also found no difference in patients treated with ticlopidine between those with diabetes requiring treatment and nondiabetics.

Therefore, we agree with Sivenius et al that diabetic patients have a different response to aspirin than do nondiabetics, although we also do not understand why. We also found decreased aspirin response in patients with elevated creatinine and severe hypertension, whereas the patients who responded best to aspirin were those who had high-grade extracranial carotid stenosis. Based on these results, we hypothesize that aspirin is less effective for patients with symptoms due to diffuse intracranial atherosclerosis, such as is commonly found in diabetics, and it is more effective in patients whose symptoms result from carotid disease. Interestingly, ticlopidine was equally effective in all of these subgroups and was particularly effective in women. Based on these data, we conclude that ticlopidine might be a better choice than aspirin in symptomatic women with diffuse intracranial disease, particularly if they are diabetic.

FIGURE 1. Bar graph showing effectiveness of acetylsalicylic acid (ASA) and ticlopidine (TIC) in diabetic versus nondiabetic patients.
already maximally dilated before they started hemodilution, which could have been done easily by testing CO₂ reactivity.

In the discussion, Korosue and Heros explained their observations by the statement that “Under such circumstances [maximal dilation of resistance vessels]. . . Hct in the microcirculation increases abruptly to the level in large vessels, with a resulting dramatic increase in blood viscosity.” To our knowledge, an observation like that has never been reported. To the contrary, under ischemic conditions a considerable decrease of Hct down to 51% of controls was observed in cortical capillaries of rabbits. Moreover, Korosue and Heros neglect to consider that the CBF response to hemodilution is completely inhibited when mean arterial blood pressure is decreased to the lower limit of autoregulatory capacity.

In addition, it is doubtful whether the grade of tissue hypoxia is comparable between the hemodilution and the hypoxic hypoxia group: Todd et al recently demonstrated that hemodilution leads to a pronounced reduction of the cerebral/arterial Hct ratio. Consequently, the hemodiluted animals will suffer from a greater reduction of cerebral oxygen-carrying capacity in comparison to the hypoxic hypoxia group, although the decrease in peripherally measured aO₂Ct was in the same range. This probably could explain the CBF response in the hemodilution group, thereby indicating that CBF was not measured in an area with complete vasoparalysis.

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References

Response
We appreciate the opportunity to respond to the criticism of our paper by Drs. von Kummer, Haag, and Back. We will address their concerns under the following headings:

1. Reason for using only relative CBF values to demonstrate the relationship between CBF and CO₂. The electrodes we used in our experiment have only a 1-mm bare tip, and the width of the rabbit cerebral cortex is about 1 mm. It is therefore very difficult to place the electrode tip completely and exclusively within the cortex. Since the blood flow in the white matter is about half that in the cortex, our CBF values almost surely represent a mixture of cortical and white matter flows; therefore, it made no sense to us to use absolute CBF values. On the other hand, because our control CBF values remained very stable for 10 hours and it is relatively well established that CBF reductions to 40% or 50% of control values cause functional impairment and maximal vascular dilation, it seemed most reasonable to use relative CBF values to demonstrate the severity of ischemia and the effects of therapy.

2. Reason for not using CO₂ inhalation to test reactivity of resistance vessels. We totally agree that CO₂ inhalation is a useful method to test reactivity of cerebral resistant vessels. However, Symon et al demonstrated that CO₂ reactivity was reduced or abolished not only in the infarcted area but also in the area immediately adjacent as well as in the intermediate zone where histological examination of the brain was virtually normal. We have enough evidence to believe that all our electrodes were located in the area in which the reduction in blood flow was severe enough to abolish CO₂ reactivity. In the ischemic control animals, the position of the electrodes was studied 8 hours after the induction of ischemia, as described in our paper. In two of the five animals, the electrodes were located outside but very close to the infarcted area; in the rest, the electrodes were located at the edge of the infarct. In the hypoxia group, hypoxic stimulation (which has a very potent vasodilatory effect) did not cause blood flow augmentation. On the contrary, hypoxic hypoxia caused a slight decrease of blood flow.

3. Dr. von Kummer and colleagues suggest that our discussion of the mechanism of blood flow augmentation in ischemic areas by hemodilution is based on a wrong assumption, i.e., that maximal dilation of resistant vessels causes an increase of hemocytometer in the microcirculation. They base this criticism on the study by Mchedlishvili and Varazashvili, which indicated that the hematocrit decreased considerably in the microcirculation under ischemic conditions. However, in that study hemocytometer was measured using histological sections prepared after in situ fixation of the brain, and only capillaries with inside diameters between 2.8 and 6.3 μm (which were large enough to contain one red cell in cross-section) were studied. They demonstrated about a 50% reduction of hematocrit in these capillaries after induction of ischemia. However, hemocytometer changes in one segment of the cerebral vasculature may not parallel changes in other segments of the microcirculation or overall tissue hemocytometer. For example, plasma skimming is one of the major factors influencing physiological hemodilution, which causes a progressive decline of hemocytometer as blood reaches the smaller vessels. This mechanical reduction in hemocytometer occurs as a result of migration of plasma to the margins of the vessel, which facilitates the movement of plasma preferentially into a side vessel. This is likely to be caused from the dynamic reduction of hemocytometer that occurs as a result of the Fahraeus effect. The magnitude of the plasma-skimming effect is dependent on both flow velocity and size of the vessel. The hematocrit decreases as the flow rate decreases in the smaller capillaries, whereas no significant flow dependency is detected in the larger capillaries and arterioles. Therefore, the implications of the observation reported by Mchedlishvili and Varazashvili are unclear. It is likely that under conditions of ischemia the hemocytometer in large capillaries is different from that in small capillaries.

Dr. von Kummer and his colleagues claim that there has been no observation of an increase of hemocytometer with a consequent increase in blood viscosity in the microcirculation under ischemic conditions. It is well known that high shear stress makes red blood cells more deformable, whereas low shear rates cause red cell aggregation. The normal state of fast flow is associated with dynamic cell deformation, whereas sluggish low-flow states are associated with massive red cell aggregation (sludge). Waltz and Sundt observed an increase in the caliber of pial arterioles with aggregation of red blood cells after occlusion of the middle cerebral artery. Although this is indirect evidence, it appears that in fact low shear rate facilitates red blood cell aggregation and increase in hemocytometer and viscosity in the microcirculation.

4. By quoting the study of Todd et al, Dr. von Kummer and colleagues claim that our hemodilution group suffered from more severe hypoxia than did the hypoxic hypoxia group. Todd et al demonstrated that isovolemic hemodilution caused a larger reduction in hemocytometer in cerebral tissue than in the peripheral vessels. This conflicts with the results of Crystal and Salem, in which isovolemic hemodilution reduced cerebral tissue hemocytometer values less than the values of the peripheral (aortic) hemocytometer. These studies imply that the ratio of cerebral to aortic hemocytometer may be different between the hemodilution and the hypoxic hypoxia...