Response

In their letter, Bladin and Burns repeat previously published arguments without considering the particulars of our study. They have cited us incorrectly several times, suggesting that they did not read our paper accurately.

1. "An absolute precision of ±0.1 mm... was... assumed by the authors." In fact, we stated that "the calipers could be adjusted in 0.1-mm graduations."

2. The "Doppler angle, which the authors omit to report..." is actually listed in Table 1.

3. "The unfortunate use of color duplex (rather than duplex-pulsed Doppler)...." We have accurately described the use of the pulsed-Doppler technique in measuring angle-corrected flow velocities. Color duplex sonography means pulsed-Doppler measurement of flow velocities in vessels that are simultaneously depicted in the B-mode scan and the superimposed color Doppler image.

4. As to "the differences in flow between the CCA and ICA+ECA...no data are given that will indicate the accuracy of an individual measurement..." Since we could not list every measurement in tables, we displayed the main data in scatterplots to make individual measurements evident to the reader. Furthermore, in Table 4 we did not only show correlations between our long-term reproducibility measurements but also the differences between them. And finally, we pointed out why we consider the measurements of ICA and ECA flow volumes more reliable than those of the CCA.

5. Duplex measurements of the ICA were not taken at the origin but at 1.0 to 1.5 cm away from the bifurcation. At this site (which corresponds to the "distal internal carotid artery site" in the paper of Ku et al) no turbulences were detectable either in the color Doppler mode or in the pulsed Doppler spectrum, and the spectral broadening index was significantly lower (p<0.0001) than at the CCA recording site (cf. Table 1 of our paper, statistic analysis unpublished). The "off axis" angle of carotid flow is of great importance at the origin of the ICA, especially when we consider maximum flow velocities or flow velocities at certain layers of flow. It is less important when time-averaged velocity (TAV), ie, the mean of all frequencies occurring above and below the baseline, is measured across the whole lumen. Given that the diameter of the vessel remains constant and a constant flow volume is transported along a vessel, TAV also has to remain constant. In this way, the TAV vector runs parallel to the walls of the vessel. Therefore, TAV must be measured with an angle correction along the walls of the vessel with the sample volume covering the entire luminal width at a site where the spectral broadening of the Doppler profile is normal. By measuring TAV in this way, we assume we have reduced--though not entirely excluded--the possible influence of non-axial flow components.

Our study is the first ever to report total CBF measurements by using color duplex sonography of the internal carotid and vertebral arteries. We think that we have provided some useful data for the clinical application of the method and future investigations, but we have also stressed that this is a preliminary study which has to be confirmed by intra- and interobserver reproducibility examinations. This study is under way and we will publish our data as soon as possible--whatever the results. There is a lack--and not abundance--in bedside methods of CBF estimation. We would be glad if "the direct methods" published 10 years ago could resolve all the technical problems. Must we wait yet another decade?

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References


Aspirin in Elderly Atrial Fibrillation Patients

Discussing their case-control study of patient features related to recurrent stroke during aspirin therapy, Bornstein et al. note that secondary analyses of the Stroke Prevention in Atrial Fibrillation (SPAF) study showed that patients over 75 years of age, particularly women, did not respond well to aspirin.1 The study by Bornstein et al and meta-analysis by the Antithplatelet Trialists' Collaboration2 do not support a differential effect of aspirin according to age or gender, and perhaps the associations we observed were spurious—play of chance enhanced by multiple comparisons. However, the SPAF study was largely a primary prevention trial in patients with atrial fibrillation, a different population with a different spectrum of stroke mechanisms.

We have subsequently undertaken a second, independent evaluation of the relation of age and gender to the risk of initial stroke in 339 patients with atrial fibrillation given aspirin in the SPAF-II study, excluding all data included in the initial analysis.1 Women over age 75 years had a risk of ischemic stroke significantly higher than that for all other patients (P<.001), younger women (P=.016), and men of equal age (P>.001).

This unexpected finding may simply reflect a high rate of stroke in elderly women with atrial fibrillation rather than a differential effect of aspirin in patient subgroups. We hypothesize, however, that elderly women with atrial fibrillation are prone to cardioembolic strokes that are not responsive to aspirin, whereas other patients with atrial fibrillation have a higher frequency of strokes related to intrinsic cerebrovascular disease that may be reduced by aspirin.

While statistical power is limited by the small number of patients (fewer than 50), is there any evidence in the data of Bornstein et al. that recurrent stroke in patients with atrial fibrillation given aspirin might be related to age, gender, or both? Perhaps an analysis including all patients with atrial fibrillation could be performed by using a Cox proportional hazards model for failure-time data, adjusting for aspirin dose, and then comparing elderly women with all others to maximize power.

On behalf of the SPAF Investigators:
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References

Response
We thank Drs Hart, Halperin, and Miller and Ms Pearce for their interest in our article on the factors associated with the failure of aspirin treatment after stroke.

Unfortunately, the small sample size of patients with atrial fibrillation does not allow us to further stratify the patients to perform multivariate analysis (Cox proportional hazards model).

As for the second point, we indeed found that ischemic heart disease is a significant risk factor for aspirin failure, since even after Bonferroni correction the odds ratio for this risk factor remains statistically significant.

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Neurobiology of Passive Avoidance Impairment After Ischemia

Karasawa et al report that passive avoidance impairment after ischemia is related to damage of CA1 neurons of the hippocampus related to memory and habituation. The neurobiology is suggested by the release of dopamine1 lateralized to the right hemisphere2 subserving passive avoidance.3 This hypothesis is supported by optimal response organization at intermediate dopamine tone in a medial-frontal-striatal activation system2 and by operant conditioning of CA1 bursting at different concentrations of dopamine, showing a sharp peak at 1 mM and falling abruptly when this optimal concentration was either halved or doubled.4 The fact that delay-dependent speeding of reaction time, indicating motor readiness, is abolished by depletion of dopamine subserving mood prompts the evaluation of ischemia-induced behavioral changes by monitoring behavioral correlates of mood, ie, speech hesitation and switching pauses.5 This method is supported by the contribution of articulatory rehearsal to short-term memory6 and by the association of >2-second speech pauses with prearticulatory repair7 and competitive and courtship activity.7 These findings suggest a causal relationship between impairment in passive avoidance and neuronal damage in the hippocampus,8 thus tending to confirm powerful isomorphisms between mind and body and the existence of deep and lawful mental structures governing human cognitive and emotional functioning reflecting properties of neuronal activity and firing.9

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References

Response
We thank Dr Friedman for his comments on our article.1

In our study, passive avoidance impairment was apparent even on day 28 after 5 minutes of induced ischemia. On that day, locomotor activity in the group subjected to the 5-minute ischemia neither increased nor decreased; rather, it was the same as in the sham-operated group. This indicates that motor function was normal on day 28 and that passive avoidance could be impaired only by mental dysfunction. In clinical studies, mental or motor dysfunction can be induced by cerebral ischemia or by stroke.2,3 However, whether the motor dysfunction in our study on ischemic gerbils reflects clinical motor dysfunction after stroke is unclear. Furthermore, passive avoidance impairment after ischemia, which may be attributed to mental dysfunction and to CA1 neuronal damage, warrants further attention for possible links to clinical symptoms. The dopaminergic system is no doubt a factor related to various behaviors. Our ongoing studies on behavioral changes after ischemia include factors related to dopaminergic systems.

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Experimental Stroke Treatment With High-Dose Methylprednisolone

We read with interest the recent article by de Courten-Myers et al.1 There are several parallels between this study and a study we recently published.2 Because ischemia is a primary pathophysiological mechanism in epidural brain compression,2 both studies involve transient regional cerebral ischemia. Both the steroids in the study by de Courten-Myers et al and the hypothesis in our study are considered to protect and resuscitate by affecting several sites along the ischemic cascade.4 In both studies treatment was initiated early, 30 minutes into the insult by de Courten-Myers et al and 15 minutes into the insult in our study. The results of the two studies are remarkably similar. In neither study did treatment decrease mortality, but in both studies treatment significantly decreased the cerebral infarct size (P<.05 in the de Courten-Myers study and P=.07 for infarct and P=.03 for overt histological damage in our study). In the de Courten-Myers study treatment clearly improved cerebral blood flow during ischemia (P<.005),
Aspirin in elderly atrial fibrillation patients.
R G Hart, L A Pearce, J L Halperin and V T Miller

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http://stroke.ahajournals.org/content/25/7/1525.citation

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