

Letters to the Editor

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Cerebral Hypoperfusion in Stroke Prognosis and Brain Recovery

The interesting report by Davis et al¹ that correlated the results of ^{99m}Tc-labeled hexamethylpropyleneamine oxime/single-photon emission-computed tomography (HMPAO-SPECT) with stroke outcome was limited to predicting the outcome only in patients with hypoperfusion demonstrated by SPECT. In 250 consecutive patients we found that three types of SPECT patterns (normal, low, and absent perfusion) had different prognostic as well as diagnostic values (high and mixed patterns associated with cardioembolism and normal perfusion with lacunar stroke) when SPECT is performed at any time within the first 5 days after the stroke onset.^{2,3} The "unexpected finding" of the significantly increased hypoperfusion between the acute and follow-up SPECT results at 3 months¹ could be explained by cystic changes that occur in chronic infarction.² It would be interesting to know the CT findings at that time. The predictive value of SPECT scanning decreases with time and has no predictive value 2 weeks after the ictus.² Furthermore, although the authors found that SPECT hypoperfusion independently predicted neurological outcome after allowing for other measures (eg, Canadian Neurological Scale [CNS] and Allen score), the increment in predictive value (ie, in R^2) was not clear. If the change is only slight, the clinical value of acute SPECT should be questioned.

The question of whether SPECT is better than clinical assessment in predicting outcome therefore remains. The combination of SPECT with transcranial Doppler (TCD) appears more promising,³ since ultrasound adds information on the degree of arterial patency. We combined semiquantitative visual SPECT patterns (normal, high, mixed, low, and absent) with TCD flow results (normal, collateral, stenotic, and occlusive) to give the cerebral perfusion index (CPI).³ This index is calculated by multiplying the arbitrary given values of SPECT and TCD patterns: CPI = SPECT pattern × TCD pattern. Compared with the CNS as a clinical predictor of recovery, the CPI performed better than clinical evaluation alone: the CPI predicted all degrees of the recovery at 2 weeks (poor, partial, good, and complete) whereas CNS differentiated only poor and partial from good recovery.³

The CPI also differentiated the reversible deficits (transient ischemic attacks and minor strokes) from deteriorating strokes within the first 6 hours.⁴ For instance, the outcome in patients with mild hemiparesis, focal hypoperfusion shown by SPECT, and normal middle cerebral arteries (MCAs) shown by TCD is better than in those with similar clinical and SPECT findings but with stenosed or occluded MCAs. TCD clearly adds an extra dimension to the prediction of stroke prognosis.

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Response

We thank Dr Alexandrov and colleagues for their comments on our article concerning cerebral blood flow measurements with HMPAO-SPECT in acute cortical infarction and brain recovery.¹ We were interested to note that Alexandrov et al found three different types of SPECT patterns, including hyperemia,^{2,3} in their patients who were studied up to 5 days. We did not see elevated cerebral blood flow, compared with the contralateral normal hemisphere, in any of our patients, who were all studied within the first 3 days of the onset of the ictus. We restricted our study to those with cortical involvement on clinical or CT scan criteria and have no experience with HMPAO-SPECT in lacunar infarction, but we are not surprised that acute perfusion is usually normal in patients with small, subcortical infarcts.

We consider that the significantly increased hypoperfusion that we observed between the acute and outcome SPECT studies at 3 months is most likely explained by early nonnutritional flow occurring in some of our acute patients. We have performed another study⁴ in which we examined the blood flow in 22 patients with acute cortical infarction less than 72 hours after onset (including 7 patients studied after intravenous streptokinase therapy) and repeated the blood flow studies in all patients at 3 months. We found that the streptokinase-treated patients exhibited a statistically greater increase in hypoperfusion between the acute and outcome studies than those not treated with streptokinase. We also found a good correlation between the size of the outcome perfusion deficits on SPECT and the volume of the tissue loss on outcome CT scans.⁴ We therefore concluded that the acute studies included a component of nonnutritional flow that might be increased by thrombolytic therapy.

Our study¹ has indeed shown that SPECT hypoperfusion adds little to clinical prognostic methods in acute stroke, but we believe that the technique provides a valuable substrate for the evaluation of therapies designed to increase perfusion to the ischemic penumbra in the acute stages of stroke.⁵ Such studies should ideally evaluate blood flow before and after the intervention, compared with controls, and also measure perfusion at the outcome stage to determine whether any reperfusion is nutritional and therefore maintained.

We were interested to hear of the authors' experience combining SPECT and transcranial Doppler measurements³ as a cerebral perfusion index in the prediction of outcome after acute stroke. It is clear that arterial blood flow in the supplying vessels and cerebral blood flow in the microvasculature may be discordant after acute stroke.⁶ For example, some patients may have branch occlusions distal to the site of intonation by TCD with normal Doppler velocities yet show hypoperfusion on SPECT. Other patients would also have tissue hypoperfusion yet have initially absent or low velocities due to proximal MCA occlusion, followed by elevated velocities due to focal MCA stenosis as recanalization occurs.^{6,7} We would certainly agree that TCD and SPECT have

complementary roles in the hemodynamic evaluation of the acute stroke patient, and it does appear that the two techniques have additive value in acute stroke prognosis.^{3,4}

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Blood Viscosity and Cerebral Blood Flow

Walzl and coworkers¹ reported an improvement of neurological function following heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) in a mixed group of acute stroke and multi-infarct dementia (MID) patients.

In the introduction the authors state that "a direct relation between plasma fibrinogen level and whole-blood and plasma viscosity and cerebral blood flow has been reported." Whereas the direct relation between plasma fibrinogen and whole-blood or plasma viscosity is well known, the relation between plasma fibrinogen (and plasma or whole-blood viscosity) and cerebral blood flow (CBF) is far from being accepted by all investigators, and in no case would it be direct but rather inverse. Even if strongly expected on the basis of the Hagen-Poiseuille law, a strict relation between blood viscosity parameters other than hematocrit and CBF has never been reported. Grotta and coworkers² found a very weak ($P=.05$) inverse correlation between fibrinogen and CBF in fifty-three heterogeneous patients; Cavestri et al³ reported significant ($P<.02$) inverse correlations between either fibrinogen or mean erythrocyte aggregation and CBF in normal subjects over 45 years but not in those under 45 years; and we⁴ were unable to find any relation between fibrinogen and CBF in three large groups—normal subjects, patients with vascular risk factors, and chronic stroke patients— independent of age. In a series of fundamental experiences,^{5,6} the group of Martin M. Brown and John Marshall clearly showed that changing blood viscosity had no significant effect on CBF, which was on the other hand strongly dependent on the oxygen-carrying capacity of arterial blood.

In their discussion, Walzl et al¹ report finding increased CBF after HELP in 10 patients not taking part in the study (5 with acute stroke and 5 with MID). As shown by Burke et al,⁷ CBF, together with neurological status, often improves between the first and second week after stroke with no therapy other than the conventional one; therefore, lacking an appropriate control

group, the CBF increase in a group of which half are acute stroke patients can hardly be considered a consequence of HELP. Moreover, the CBF parameter considered in this article (which is likely to be the gray-matter flow because values are expressed as milliliters per 100 grams per minute) may be misleading in low-flow conditions, such as those reported in the article (from a mean±SD value of 44.3 ± 9.4 , values as low as 30 or 35 mL/100 g per minute can be derived). In this respect, analysis of initial slope index (ISI)⁸ is more reliable, but ISI values are not reported in the article. Toward this purpose, one study⁹ failed to find changes of CBF (ISI) following LDL apheresis despite a significant drop in fibrinogen, LDL cholesterol concentrations, and whole-blood viscosity (low shear) in a small group of familial hypercholesterolemics.

Finally, if (as the authors suggest) HELP has caused a lipoprotein and fibrinogen reduction that leads to a CBF increase, the two phenomena should in some way be correlated; this, however, is not mentioned in the article. Although we found both reduced CBF and increased fibrinogen and plasma and whole-blood viscosity in cerebrovascular disease patients, we did not obtain significant correlations between each of the hemorheological variables and CBF.¹⁰ Indeed, CBF could become dependent on blood viscosity in individual patients whose cerebral regions have a strongly impaired CBF autoregulation, as demonstrated in animals,¹¹ but this was not shown by the authors.

In conclusion, although we appreciate the effort to support the hemorheological approach to therapy of cerebrovascular disease, the discussion seems to be mainly based on the assumption that clinical improvement observed after HELP can be mediated by increased CBF, which is not clearly supported by the results and needs an ad hoc study design, since conflicting data are present in the literature.

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