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What Is the Predictive Value of Increased Technetium-99m-HMPAO Uptake for Brain Survival/Necrosis in the Acute Stage of Ischemic Stroke?

TO THE EDITOR: To determine the predictive value of early SPECT imaging for tissue outcome, Shimosegawa et al. (*1*) retrospectively compared ^{99m}Tc-HMPAO SPECT scans obtained within 6 hr from onset of ischemic stroke in the carotid artery to cerebral infarction topography as assessed by CT scanning. Their conclusion that profoundly reduced HMPAO uptake is predictive of final infarction agrees with our own findings with quantitative PET imaging of cerebral blood flow (*2,3*) and indicates that SPECT imaging in the acute stage of stroke could be clinically useful to predict a (minimum) size for final infarction. In turn, this may help in the individual selection into trials of those patients most likely to significantly benefit from therapy (*4*).

Shimosegawa et al. also report focally increased HMPAO uptake in three patients and claim that these areas were consistently infarcted on control CT scans. This finding conflicts with our experience in 11 patients with focal hyperperfusion. These patients form a subset of a larger sample prospectively selected for MCA territory stroke without signs of hemorrhage on admission CT scans, studied with PET within 5–18 hr after stroke onset and followed-up for spontaneous evolution. In each of the 10 survivors in this subset, the CT scan obtained during the chronic stage (30–60 days postonset) revealed that the initially hyperperfused areas were eventually intact structurally (*5,6*), suggesting that early hyperperfusion (i.e., the hallmark of efficient postischemic reperfusion) is not only harmless, but actually presumably beneficial, to brain tissue. In the nonsurvivor, whose death at 10 days from massive brain infarction precluded exact assessment of tissue outcome (an autopsy was refused), the area of hyperperfusion lay on the borders of a large area of near-zero perfusion and oxygen metabolism and exhibited values for the latter far above the accepted threshold for irreversible damage (*2*), suggesting it reflected branch recanalization on the border of an established infarct.

There are two brief accounts of HMPAO studies performed within 48 hr of stroke onset that tend to support our findings. Baird and Donnan (*7*) found that regions of increased HMPAO uptake in 11 patients usually had normal CT topography at 7–14 days. Sperling and Lassen (*8*) observed that increased HMPAO uptake within 48 hr of stroke onset is uncommon and tends to occur in regions without infarct on CT performed at a later date.

The apparent conflict between our findings and those of Shimosegawa et al. might be related to methodology. As compared to our prospective study, in which we performed chronic-stage CT scanning in strict coregistration with PET, the CT in the Shimosegawa et al. study was performed 2–10 days after stroke—a suboptimal time to assess the exact borders of infarction due to vasogenic edema and mass effect. Moreover, the plane for SPECT was manually adjusted to be parallel to the orbitomeatal line to match the CT plane, a posthoc procedure with disputed accuracy. The only patient for which they showed illustrations had the rare event of a stroke in the anterior cerebral artery territory, preceded by a left occipital hemorrhage. This patient's CT scan 7 days postinfarct showed changes not suggestive of complete tissue necrosis. Furthermore, it is unclear whether at least one of their three patients was subjected to intra-arterial thombolysis (either before or after the SPECT study), a procedure which might have interfered with the spontaneous course of events. Finally, previous work has shown that increased HMPAO brain uptake after stroke does not always reflect true hyperperfusion (*9,10*), presumably because the mechanisms for trapping HMPAO in the brain tissue depend on the blood-to-brain pH shift and thus on barrier integrity and tissue metabolism, both of which can be disrupted after stroke. Another difference between the Shimosegawa study and ours refers to the time of investigation from stroke onset (less than 6 and from 5 to 18 hr, respectively), so that we may have seen different events, but there is no current evidence for this.

Overall, we believe Shimosegawa et al.'s observations about HMPAO hot spots early after stroke raise an important issue but need to be replicated in a prospectively designed investigation, preferably with a true perfusion tracer such as ^{133}Xe. They may have observed a new, although in all likelihood rare, event consisting of early hyperperfusion associated with tissue necrosis, but this requires thorough confirmation.

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REPLY: Although ^{99m}Tc-HMPAO SPECT CBF imaging within 6 hr after onset of ischemia has been verified, its predictive value for morphological change in hypoperfused areas (*1*) and positive uptake of tracer flow to the affected area in the very early stage of cerebral infarction has not been evaluated in detail. In addition, its physiological meaning for tissue outcome is obscured. Marchel et al. (*2*) conducted PET studies in 18 patients with cerebral infarction 5–18 hr after stroke onset and found that 6 patients who showed increased perfusion demonstrated fewer changes in oxygen consumption and had good neurological outcomes. Although there was no presentation of CT or MRI findings, they concluded that hyperperfusion in the early stage of infarction would become a landmark for better clinical outcome, which reflects early spontaneous recanalization of occluded vessels. Based on morphological data, we have found that areas with high uptake on early ^{99m}Tc-HMPAO SPECT images returned to necrotic tissue on follow-up CT studies (*1*).

Obviously, these evaluations cannot compare directly because of the different methodological backgrounds and the two patients we present would be suggestive of considering these discrepant consequences. One patient was reported in a previously published study (Fig. 1) (*1*). MR or CT-guided segmentation and registration methods make it possible to match SPECT or PET images precisely to infarcted and peri-infarct areas (*3*). Matched and resliced SPECT images obtained during the early stage of cerebral infarction (examination time was 2.4 hr after onset) show areas with hyperperfusion that undoubtedly correspond to the completely necrotic areas on the reference CT image obtained during the chronic stage. Figure 2 depicts the registered and matched initial [^{123}I]IMP SPECT images of another patient, which indicate markedly increased uptake within the completely infarcted area, as determined by reference MRI in the chronic stage. Although neither patient underwent thrombolytic therapy throughout their clinical courses, they did experience a partial improvement of clinical symptoms before admission. Moreover, cerebral angiography of these patients, immediately after initial SPECT scanning, depicted early spontaneous recanalization of the occluded vessels. Consequently, only addressing methodological questions in our previous work (i.e., mismatch between SPECT and reference CT images, choice of staging for reference CT and change in the fractional fixation of tracer) (*4–6*) would not give a complete answer for these findings.

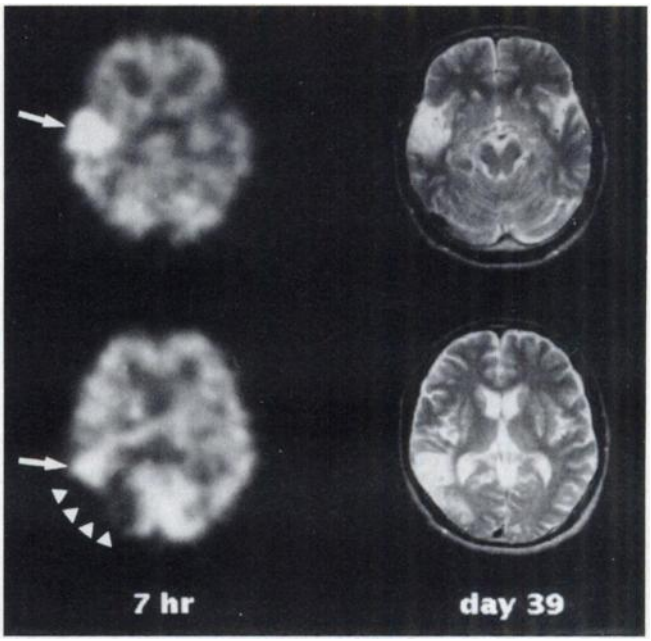

FIGURE 2. A 71-yr-old man with sudden onset of left hemiparesis and hyperesthesia. Hyperperfused (arrow) and hypoperfused areas (arrowheads) on [^{123}I]IMP SPECT CBF images obtained 7 hr after onset (left column) are consistent with completely infarcted areas on follow-up T2-weighted MR images obtained in the chronic stage of infarction (Day 39, right column). All SPECT CBF images were registered and resliced after matching to follow-up CT.

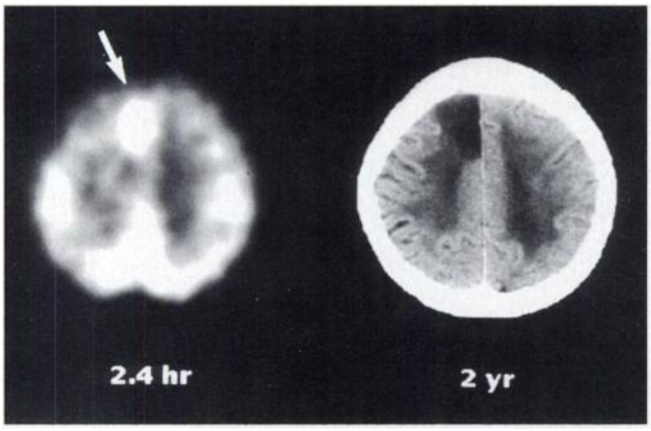

FIGURE 1. A 76-yr-old woman with sudden onset of left hemiparesis and dysarthria. Technetium-99m-HMPAO SPECT CBF image obtained 2.4 hr after the onset (left) and follow-up CT image obtained 2 yr after onset (right) show good correspondence between the hyperperfused area (arrow) and necrotic tissue in the chronic stage of infarction. The SPECT CBF image was registered and resliced after matching to follow-up CT.

Although the reason for excess blood flow in the early stage of ischemia has not been definitively elucidated, tissue acidosis and/or accumulation of free radicals in the extracellular space, which are known to progress within this time range (*7–9*), are important bases for increased CBF. Biphasic uncoupling of CBF and oxidative metabolism during reperfusion in an experimental model of severe ischemia would be compatible with the pathophysiology (*10*). Postischemic hyperemia with and without persistent metabolic impairment could occur within several hr after vessel occlusion and subsequent reperfusion. Moreover, the severity of metabolic derangement with hyperemia was observed in this profound ischemic model. Another report, however, has pointed out that only incomplete correlation was found between postischemic hyperemia and the degree of preceding ischemia (*11*).

Although vasodilating factors after ischemia generally originate from the derivatives of cell damage, these are primarily effective on the circulation control of the brain and resultant change of CBF is sometimes incongruous with metabolic change. It is conceivable that early postischemic hyperemia would be more related to clinical improvement than tissue viability itself. We and other authors