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Paradoxical Hyperfixation of HMPAO in Cerebral Infarction

Single-photon emission computed tomography (SPECT) of the brain has been gaining widespread acceptance as a clinical method for assessing regional cerebral blood flow in a variety of clinical settings (1). Perhaps it has been studied most extensively in the context of stroke and cerebrovascular disease, which includes evaluation of its effectiveness in diagnosing and subtyping acute stroke (2) and assessing transient ischemic events (3).

In the real world of the emergency center, therapeutic decisions for acute stroke are often challenging. Brain SPECT has been shown to be highly predictive of hemorrhagic transformation (4). Acute SPECT has been successful in predicting intracranial bleeding in patients receiving thrombolytics (5, 6). SPECT has been shown to add substantial prognostic information when compared to conventional clinical assessment (7). Increased or normal tracer uptake is associated with a good prognosis (7, 8), and may indicate when spontaneous recanalization has already occurred. Such spontaneous reperfusion may occur in as many as one-third of all patients with embolic stroke (9). Large clinical trials are underway in several centers to evaluate further the role of acute SPECT in clinical management (10).

In this setting, the case reports by Shintani et al (11, 12) raise a troubling specter. They present four cases in which increased uptake of the SPECT perfusion tracer is seen in or near areas of acute infarction. They suggest that this reflects localized hyperfixation of the tracer, ie, tracer uptake is not reflective of the actual state of brain perfusion. They claim that this "paradoxical" tracer uptake does not reflect spontaneous recanalization or a physiologic increase of blood flow. Why is this important? If correct, these findings would imply that SPECT is unreliable in the setting of acute stroke. Although, for subacute strokes, this would be of primarily academic interest, it is a critical point if SPECT is to be used in acute patient management. If the scan suggests increased perfusion in a region that is actually ischemic, therapy would be mistakenly withheld at great potential loss to the patient. Unfortunately, only one of the patients reported by Shintani was imaged within the time frame in which aggressive therapy would actually be considered.

Hyperfixation of tracer, with more uptake than "appropriate" for the level of regional perfusion, has been reported previously in the subacute setting (13), but never in acute stroke. Hyperfixation differs importantly from hyperperfusion or "luxury perfusion." In the one case, the SPECT scan misleads the clinician. In the other, it accurately depicts physiology. In their letter, Patterson et al (page 941)

appropriately challenge Shintani's assertion that uptake in the cases reported was actually hyperfixation. In order to prove that tracer uptake did not reflect actual perfusion, some independent measure of perfusion (eg, angiography, xenon SPECT, perfusion MR imaging) must be employed. The scan cannot be deemed an incorrect measure unless we know that perfusion was not in fact increased in these patients.

Shintani used no independent measure of brain perfusion at the time of SPECT imaging. He claims that spontaneous reperfusion was clinically unlikely. This is a difficult assertion to prove. Of the four patients reported, two had embolic strokes, a subtype with a high incidence of spontaneous reperfusion. One patient had a normal angiogram 13 days after the event, and therefore certainly had spontaneous reperfusion at some point. The only patient with proved vascular occlusion did not have a SPECT scan until 5 days after symptom onset. Hyperemia due to "luxury perfusion" is well known to occur within this time frame and does not imply hyperfixation. Although Shintani suggests that the clinical course of his patients did not indicate early recanalization, it is well known that recanalization does not necessarily result in observable clinical improvement, and may, in fact, occasionally be associated with clinical worsening caused by edema and other problems.

If hyperperfusion were rare in acute stroke, then it might be correct to assume that any increased tracer uptake seen reflected "paradoxical hyperfixation" of tracer. It is not, however, rare. A quantitative PET study by Marchal et al (14) found that at least 10 of 30 patients studied in the period 5–18 hours after symptom onset had marked increases in local cerebral perfusion, averaging 74% higher than the contralateral side. Transcranial Doppler imaging did not show vascular occlusion in any of these patients. The areas of hyperperfusion tended to be primarily cortical and adjacent to, but distinct from, the eventual infarct territory. Interestingly, in all cases reported by Shintani, the increased uptake appears centered in the cortex rather than the deeper sites of eventual infarction. These images are strikingly similar to those of Marchal's report.

It is clear from the work of Marchal and others that hyperperfusion is a common finding in the first day of a stroke, and that it is frequently associated with a good tissue outcome. Early hyperperfusion may, in fact, be a marker of early recanalization. Thus, the increased SPECT tracer uptake reported by Shintani may be explained well on the basis of actual increases in local perfusion rather than "paradoxical hyperfixation." Although superimposed hyperfixation cannot be excluded, compelling evidence for it has yet to be presented.

Future studies of the possibility of hyperfixation using independent measures of perfusion would certainly be of interest. Even more relevant will be the results of the ongoing large-scale clinical trials of SPECT in the acute setting. Pending the results of these studies, it seems most reasonable to suppose that the increased tracer uptake seen in some patients with very acute stroke is a reasonably reliable indicator of actual physiology and frequently represents an area of spontaneous reperfusion hyperemia.

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