Hyperfication of HMPAO in Subacute Ischemic Stroke Leading to Spuriously High Estimates of Cerebral Blood Flow by SPECT

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We want to report an error in interpreting d,l-hexamethylpropylene amine oxime (HMPAO) tomograms as cerebral blood flow (CBF) in subacute ischemic stroke cases. By simultaneously studying CBF by $^{133}$Xe dynamic single-photon emission computed tomography (SPECT), an obvious discrepancy was noted in that the HMPAO tomograms grossly exaggerated the reflow hyperemia following spontaneous reperfusion.

To interpret $^{99m}$Tc-HMPAO images in terms of CBF distribution, it is essential that the same or almost the same fraction of locally supplied tracer is fixed in the various regions, healthy as well as diseased, at the time imaging is performed. This fixation is due to extraction across the blood–brain barrier (BBB) and to retention of the extracted tracer molecules, a retention caused by chemical conversion to a hydrophilic metabolite that is unable to cross cell membranes as well as the BBB. A constant degree of fractional fixation in all brain regions of 40–50% has been found in humans. 

A few series comparing $^{99m}$Tc-HMPAO images with CBF tomography obtained by $^{133}$Xe as well as with $^{123}$I positron emission tomography images have consistently shown a good agreement in normal humans and in various disease states including acute ischemic stroke, but the number of such comparisons is rather limited. Nevertheless, the impression gained from this factual basis is that $^{99m}$Tc-HMPAO can be trusted to image CBF distribution after correction for a minor nonlinearity due to back-diffusion in the first few minutes. The fidelity of $^{99m}$Tc-HMPAO to map CBF has been taken for granted to such an extent that it has been used as a “gold standard” of CBF distribution in comparative studies with other SPECT tracers of CBF such as N-isopropyl-p-($^{123}$I)iodoamphetamine ($^{123}$I-IMP) or $^{99m}$Tc-($^{99m}$Tc-N$_2$N$'$-1,2-ethylenediyldibis-l-cysteine diethyl ester ($^{99m}$Tc-ECD).7

We report here three cases of focal hyperfixation of $^{99m}$Tc-HMPAO in patients with subacute stroke (2–3 weeks) with evidence of infarct reperfusion. By hyperfixation we mean a higher counting rate over the infarct (relative to that of the opposite side) than can be explained by CBF as measured by $^{133}$Xe tomography at the same time. This can only occur if the fractional fixation exceeds the normal level of 40–50%.

In case 1, on October 26, 1992, a 62-year-old man suddenly developed massive right-sided hemiparesis and aphasia. On day 3, SPECT with $^{99m}$Tc-HMPAO showed massive reduction of tracer uptake in the anterior half of the left middle cerebral artery (MCA) distribution territory. When restudied on day 15, we first measured CBF by $^{133}$Xe tomography. As shown in Figure 1, the infarct area (seen as a large computed tomographic hypodensity) had largely reperfused, with CBF values only slightly below those of the healthy side, resulting in an infarct-to-control-region ratio (infarct/control ratio) averaging 0.94. $^{99m}$Tc-HMPAO injected 20 seconds after completion of the $^{133}$Xe study, at a time of unchanged blood pressure and end-expiratory Pco$_2$, showed, on the other hand, an increased uptake of $^{99m}$Tc-HMPAO in the infarct. The $^{99m}$Tc-HMPAO infarct/control ratio averaged 1.25, implying a local hyperfixation of 1.33 (1.25/0.94), i.e., 33% above that of the opposite side. Therefore, if the fractional fixation of the nonaffected side were 45%, that of the infarct had risen to 60% of the amount of tracer supplied by the blood flow. Thus, the moderate degree of reperfusion, with flow below that of the healthy control region, was grossly overestimated by the $^{99m}$Tc-HMPAO tomogram that indicated a reperfusion hyperemia of 25% above that of the control region.

We subsequently studied two other subacute ischemic stroke cases with $^{133}$Xe evidence of infarct reperfusion. Both had infarct regions of high $^{99m}$Tc-HMPAO uptake, with side-to-side counting ratios exceeding that of CBF by $^{133}$Xe. In these cases, focal hyperfixation of 13% and 19% were recorded.

These findings clearly show that the idea of a constant fractional fixation of $^{99m}$Tc-HMPAO in various forms of diseased tissue cannot be upheld. Intuitively, one would have guessed that some forms of altered brain tissue (infarcts, tumors) would perhaps be unable to retain $^{99m}$Tc-HMPAO as well as normal tissue. Due to the resultant excess loss of tracer by back-diffusion, we consequently have been on the outlook for focal hypofixation by comparing $^{133}$Xe with $^{99m}$Tc-HMPAO. To date we have not seen this.

On the other hand, we had not envisaged hyperfixation. Hence, having for several years noted the “hot spot” of high $^{99m}$Tc-HMPAO in many ischemic stroke cases studied 1–4 weeks from onset, we, as others, felt confident that this represented hyperemia, a state of “luxury perfusion.” This is not so. The high $^{99m}$Tc-HMPAO uptake in the

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infarct region undoubtedly represents a state of reperfusion, but the hyperemia is in many cases more moderate than is indicated by the $^{99m}$Tc-HMPAO count rate ratio. Clearly, the use of a linearization algorithm to correct for back-diffusion is not applicable in these cases. Further systematic studies involving proper protocols and patient consent are planned to elucidate when hyperfixation sets in and stops.

References

FIGURE 1. Case 1. Slices are cut parallel to and 50 mm above the orbitomeatal plane. $^{133}$Xe inhalation tomography (left panel) shows slight hypoperfusion in all of the left middle cerebral artery territory (relative to that of the nonaffected hemisphere), whereas a relatively high $^{99m}$Tc-d,l-hexamethylene-propylene amine oxime (HMPAO) uptake in the same region is seen (right panel). This area of HMPAO hyperfixation corresponded exactly to the area of infarction seen on computed tomographic scanning.

(2600)
Absolute flow maps (ml/100g/min)

Stroke + 15 days

DISTRIBUTION IMAGES (COUNTS/10SQMM)

Xe-133 inhal. flow study, interl. 4.
Slice 2, 50mm

SPECT & LASSEN/1992

HMPAO Tc-99m STUDY
Slice 5, 50mm

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Hyperfixation of HMPAO in subacute ischemic stroke leading to spuriously high estimates of cerebral blood flow by SPECT.

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