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## Reply

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*AJNR Am J Neuroradiol* 1999, 20 (5) 946

<http://www.ajnr.org/content/20/5/946>

This information is current as  
of May 12, 2025.

# Another Spurious Description of Hyperfixation of HMPAO

Shintani and colleagues (1) describe four cases of cerebral infarction in which single-photon emission computed tomography (SPECT) imaging of cerebral perfusion was performed using hexamethylpropyleneamine oxime (HMPAO). The authors conclude that "hyperfixation (of HMPAO) can occur in all stages of infarction, and does not appear to depend on recanalisation." An examination of the evidence presented by the authors to support this statement is merited, particularly in light of recent calls for increased use of this important imaging technique for stroke (2).

SPECT scans were acquired at the following times after symptom onset: case 1—4 hours; case 2—2, 7, and 20 days; case 3—17 days; and case 4—5 and 16 days. Therefore, in only one case, and for only one SPECT scan (case 1), do the findings relate to what now is considered to be the acute stage of stroke when thrombolytic and neuroprotective therapy are to be most effective. The authors admit that this particular patient was the subject of a previous single case report (3), but what is more disconcerting is their failure to refer to the criticisms published in this journal of their use of the term "spurious hyperfixation" in that article (4, 5).

We believe it is unnecessary to repeat all of the points we made in our previous correspondence (4). Nonetheless, we reiterate that the term "hyperfixation," when applied to the uptake of HMPAO, refers to a proved phenomenon (6, 7) that occurs in the late subacute stages of stroke (10 to 28 days after onset). Furthermore, the uptake of HMPAO is higher than would be expected from the true level of CBF. This overestimation may be present even when the uptake is below that of the adjacent or contralateral normal tissue, and, on average, is equal to about 20% of the expected value (7). In the earlier stages of stroke (up to 10 days) Sperling and Lassen (7) quite categorically stated that no hyperfixation was present even when HMPAO uptake was increased.

The existence of hyperfixation can be substantiated only when HMPAO SPECT is performed in conjunction with a "gold standard" method of measuring blood flow, such as  $^{133}\text{Xenon}$  SPECT or  $\text{C}^{15}\text{O}_2$  PET. Shintani and colleagues did not perform such measurements, and cannot claim that hyperfixation exists in any of their cases.

What the authors did find was high uptake of HMPAO in areas of the brain, which eventually were associated with tissue loss on structural images. The authors readily jump to the conclusion, as they did in their previous publication (3), that this represents paradoxical hyperfixation. Of course, this finding has two possible explanations: 1) it is caused by a high CBF (hyperperfusion), or

2) it occurs in an area of low CBF, but where the trapping of HMPAO is enhanced (hyperfixation).

Reperfusion hyperemia has been described in many classic studies (8–10) in both the acute and subacute stages of stroke. Whether this hyperfusion is beneficial (nutritional) or nonnutritional, and thus whether the region involved progresses to infarction, depends on the magnitude of the initial ischemia and the timing of the reperfusion. In either situation, it represents a true increase in cerebral perfusion demonstrable by PET with  $\text{C}^{15}\text{O}_2$  (11) and SPECT with  $^{133}\text{Xenon}$  (12). It is present in a region consistently much larger than the area of infarction seen in later structural imaging, although within this region there may be smaller areas of poorly perfused tissue that cannot be detected by poor resolution imaging systems, such as the one used by the present authors.

The mere existence of high HMPAO uptake in any stage of stroke does not necessarily imply hyperfixation of this tracer, yet that appears to be the premise of this article. The only explanation for the conclusion drawn by the authors is that they have made the assumption that because the tissue has progressed to infarction, then cerebral blood flow must have been low during the SPECT scans. Published literature on hyperperfusion attests to the naiveté of such an assumption, even in subacute stroke.

It is disappointing that the authors have been allowed to repeat such an unscientific approach to an important subject. Hyperfixation of HMPAO is a phenomenon that should be considered as one of the possible causes of increased uptake of HMPAO in subacute stroke. It has never been shown to present in acute stroke, when the use of HMPAO SPECT is likely to be most effective. At both time periods, HMPAO SPECT continues to be a reliable indicator of reperfusion, even when hyperfixation is present (7).

Further investigation of hyperfixation should be encouraged at centers equipped to perform such studies.

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### Reply

We apologize that we did not perform the "gold standard" method of measuring CBF— $^{133}\text{Xe}$  SPECT. Nonetheless, we think that the "hyperfixation of HMPAO" is not caused by high CBF (hyperperfusion), but occurs in an area of low to slightly high CBF where the trapping of HMPAO is enhanced. First, the HMPAO SPECTs were performed in our study (1) 4 hours (case 1), 2, 6, and 19 days (case 2), 17 days (case 3), and 5 and 16 days (case 4) after the onset of stroke, respectively. The paradoxical hyperfixation appeared in every stage in cerebral infarction: extremely acute stage (4 hours in case 1); earlier acute stage (2 days in case 2); delayed acute stage (6 days in case 2, 5 days in case 4); and subacute stage (19 days in case 2, 17 days in case 3, and 16 days in case 4).

In case 1, the radiotracer counts in the region of interest (ROI) in the area of HMPAO hyperfixation and the corresponding region of the contralateral hemisphere averaged  $195.3 \pm 17.6$  vs  $42.7 \pm 1.4$  and  $145.3 \pm 10.0$  vs  $41.3 \pm 3.0$ , respectively (1). The tracer counts of ROIs in hyperfixation are four to five times higher than those of the normal region. True CBF of reperfusion hyperemia cannot be so much.

In case 2, on day 3, 2 days after the onset of stroke of the left middle cerebral artery (MCA), HMPAO SPECT showed unexpected hyperfixation in the left hemisphere (Fig 1A) during the period when the patient deteriorated to deep coma and required intubation. Clinical manifestations did not suggest recanalization in case 2 on day 3. Moreover, the HMPAO hyperfixation in the area of infarct persisted for a long time—2 days (Fig 1A), 6 days (Fig 1B), and 19 days (Fig 1C) after stroke

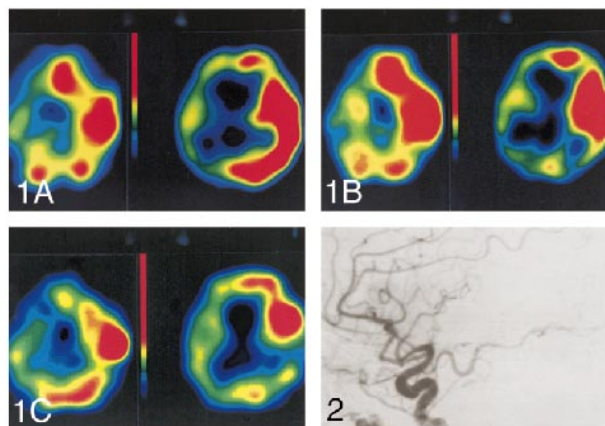


FIG 1. HMPAO SPECT 2 days (A), 6 days (B), and 19 days (C) after stroke onset (Case 2).

FIG 2. Angiography shows occlusion of the temporoparietal branch of the MCA (Case 3).

onset. On day 13, cerebral angiography revealed normal filling of the MCAs and anterior cerebral arteries bilaterally suggesting recanalization of the left MCA. Clinical manifestations and angiographic findings suggested that recanalization occurred between day 4 and 13. Serial hyperfixations of HMPAO in case 2 were not attributed to recanalization of the vessels.

Likewise, in case 3, cerebral angiography revealed the occlusion of the temporoparietal branch of the left MCA without evidence of recanalization (Fig 2). We think that hyperfixation can occur in all stages of infarction, and does not appear to depend on recanalization (1).

The mechanism of HMPAO hyperfixation in infarction is not known.  $^{99\text{m}}\text{Tc}$ -d, 1-HMPAO is the first clinically available  $^{99\text{m}}\text{Tc}$ -labeled CBF retention tracer. The cerebral retention of  $^{99\text{m}}\text{Tc}$ -HMPAO is believed to involve the intracellular conversion of the hydrophobic Tc-HMPAO to a species that is incapable of rapid back diffusion (2). The proposed mechanism of this conversion is thought to involve interaction of  $^{99\text{m}}\text{Tc}$ -HMPAO with glutathione (GSH) (3). GSH is responsible for intracellular trapping. Neirinckx et al suggested the accumulation of  $^{99\text{m}}\text{Tc}$ -meso-HMPAO was dependent more on GSH content than blood flow (4). In acute and subacute stages of cerebral infarction, increased GSH levels may result in increased HMPAO retention.

Spurious hyperfixations in cerebral infarction probably happen less in  $^{99\text{m}}\text{Tc}$ -ECD and Iodine-123-iodoamphetamine SPECTs than in HMPAO SPECT.

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### Three-Dimensional Power Doppler Imaging of Vertebrobasilar Circulation in Adults

Development of a three-dimensional (3D) sonographic technique has enabled delineation of fetal surface features, abdominal organs, and coronary arterial walls (1–5). Power Doppler imaging is more sensitive in detecting blood flow signals than is color Doppler. Kenton and colleagues reported that power Doppler offered significant advantages over color Doppler in the imaging of intracranial cerebral arteries (6). By a combination of power Doppler and 3D technology, it is possible not only to image small vessels, but also to construct 3D images of vascular structures. In this communication we show vertebrobasilar arteries imaged by 3D power-Doppler imaging.

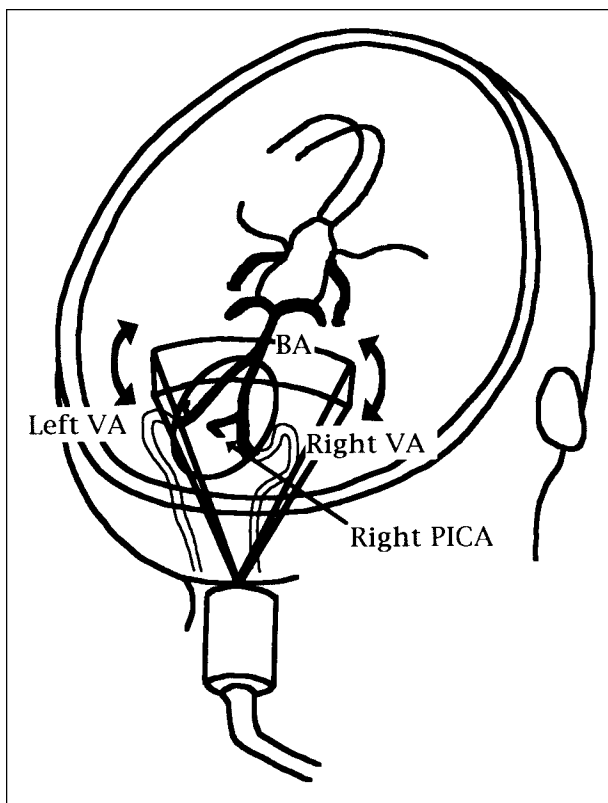


FIG 1. Schema shows relationship between transducer and vascular anatomy. The transducer was placed between the squama occipitalis and the palpable spinous process of the first cervical vertebra. After detecting blood flow signals from the VA, bilateral PICAs, and the BA by 2D power-Doppler imaging, the transducer was locked back and tilted very slowly to assess these arteries. Subsequently, by using a 3D digital system, 3D power-Doppler images of the vertebrobasilar arteries were reconstructed after rendering.

We applied a 2D and 3D power Doppler examination for the imaging of a 22-year-old healthy woman with the HDI 3000 (Advanced Technology Laboratories, Botnell, WA). The 3D imaging rendered a volumetric vessel appearance with power Doppler. Using power Doppler, we acquired flow data in a 2D slice through a volume of the vessel and represented spatial relationships within that 2D plane. We reconstructed the 2D plane data into the 3D power Doppler image. During this process, parenchymal data were subtracted. The transducer was a digital broadband steered phased array with frequencies ranging from 2–3 MHz for B-mode imaging and Doppler functions. Our patient was examined in the lateral decubitus position. The transducer was placed between the squama occipitalis and the palpable spinous process of the first cervical vertebra, and the Doppler beam was aimed at the bridge of the nose. We detected blood flow signals from the vertebral arteries (VAs), the posterior inferior cerebellar arteries (PICAs), and the basilar arteries (BAs) in real time, which were displayed as color signals within a subsector of the black-and-white image by using 2D power Doppler. Then, the transducer was locked back and tilted very slowly to image VAs (V3–V4 segments), PICAs (bilateral views), and the BA (proximal view) for 15 seconds, and collect and store 74 images in the computer memory. Subsequently parenchymal data were subtracted and a rendering of the vascular anatomy was composed with a 3D digital system. Then, 3D power Doppler images of the vertebrobasilar arteries were reconstructed. In addition, 15 images could be displayed selectively on a video monitor in dynamic partial rotation to enable viewing from

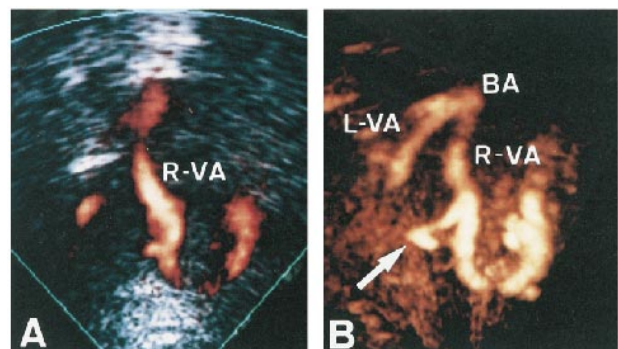


FIG 2. 2D and 3D power-Doppler images.

A, 2D power-Doppler image shows the right VA (segments V3–V4), part of the PICA, and the left VA.

B, 3D power-Doppler study clearly depicts the VAs and the PICA branching from the right VA (arrow).



different angles within the spatial range of 110°. Figure 1 shows the transducer placement and the anatomic structures.

The 2D power Doppler image showed the right VA (V3–V4), part of the right PICA, and the left VA (Fig 2A), but it could not show the entire vertebrobasilar system continuously. The 3D power Doppler method, however, clearly and continuously imaged the VA, and displayed a 3D image of the BA (Fig 2B).

Clinical application of the 3D power Doppler method, when applied with meticulous technique and improved technology, may enable visualization of vascular diseases such as aneurysms, arteriovenous malformations, and other vascular disorders of the vertebrobasilar system.

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### Endovascular Aneurysm Treatment and the Incidence of Vasospasm

The article by Yalamanchili et al (1) and the accompanying editorial by Charles Strother (2) in the *AJNR* regarding the frequency of cerebral vasospasm after endovascular occlusion of intracranial aneurysms were interesting. Nonetheless, I would caution readers about too readily drawing the conclusion that endovascular treatment is less likely to cause symptomatic vasospasm (delayed ischemic neurologic deficit) than surgery after treatment for aneurysmal subarachnoid hemorrhage.

The study was retrospective, the patient population was small, and the use of matched patient series is fraught with potential unrecognized selection biases. To draw firm conclusions from such data is unreliable. As the authors point out in their conclusion, there is an overriding need for properly conducted prospective randomized studies in this area, and we strongly agree with Dr. Strother's call for a prospective randomized clinical trial to begin in the U.S.

Such a trial is underway in the rest of the world. The International Subarachnoid Aneurysm Trial (ISAT) has been running a full-scale study since January 1997 and has been a pilot study since 1994. The study is funded by the UK Medical Research Council, the Canadian Medical Research Council, and the UK Stroke Association for Neuropsychological Assessment. Nineteen centers are participating in the UK, Europe, Canada, and Australia, and over 550 patients have been randomized in the study. The numbers required to fulfil the pri-

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### Acknowledgments

This work was supported by the Research Grant for Cardiovascular Diseases (8-C4, 9-A2) from the Ministry of Health and Welfare. The authors would like to thank Mr. Juni Warabino for technical assistance and Ms. Yuki Iwakiri for cooperation with the present study.

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mary objective are between 2000 and 3000 patients. One of the issues that will be addressed in a systematic manner will be the incidence of delayed ischemic impairment (vasospasm) in the two groups of patients. The trial is likely to continue recruiting until 2000 and report in 2001.

The aims of the trial are to compare the safety and efficacy of an endovascular treatment policy of ruptured intracranial aneurysms with a conventional neurosurgical treatment policy in an eligible population. Our primary objective is to determine whether an endovascular treatment policy of acutely ruptured intracranial aneurysms, compared with a neurosurgical treatment policy, reduces the proportion of patients with a moderate or poor outcome (defined by Rankin grade 3–6) by 25% at 1 year. Secondly, we will seek to determine whether endovascular treatment is as effective as neurosurgery in preventing rebleeding from the treated aneurysm, results in a better quality of life than neurosurgery at 1 year (Euroqol measure), is more cost-effective than neurosurgical treatment, and improves the neuropsychological outcome at 1 year (UK centers). Finally, we will examine outcomes over 5 years, with specific reference to rebleeding rates, to determine the long-term significance of angiographic results.

Our study is an open, randomized, controlled clinical trial of patients with acute subarachnoid hemorrhage from a ruptured aneurysm who are admitted to participating centers and in whom their treating physician is uncertain whether an endovascular or neurosurgical treatment is best for them.

Randomization to an endovascular or neurosurgical treatment policy is conducted via a 24-hour telephone service provided by the clinical trials services unit at the coordinating center. Appropriate minimization criteria is set to ensure balance of known risk factors between the two treatments. The details and progress of the trial were the subject of a poster presentation at the SNR/ASNR in Philadelphia. We would strongly encourage and support our U.S. colleagues to carry out a similar study that we regard as essential to determine the best management of patients with aneurysmal subarachnoid hemorrhage.

### Direct Angioplasty for Acute Occlusion of Intracranial Artery

We have read with interest an article by Nakano et al published in the *AJNR* regarding direct percutaneous transluminal angioplasty for acute middle cerebral artery (MCA) occlusion (1). The authors report their experience with using direct percutaneous angioplasty (PTA) as the sole means of treating 10 patients with acute MCA occlusion when initial CT scans show early ischemic changes, lenticulostriate artery (LCA) involvement, or both. The authors' rationale for choosing direct PTA alone to establish blood flow without using thrombolysis is based on the high risk of hemorrhagic complications in this group of patients. The authors believe that such a risk can be reduced by avoiding thrombolytic therapy. The angiographic success rate in their patients was relatively high (80%), and there were no hemorrhagic complications; however, the rationale for their method becomes debatable despite a high rate of angiographic success without hemorrhagic complications.

We wonder whether the authors may have overlooked the fundamental disease process that causes hemorrhagic complications during acute ischemic stroke. Patients with early ischemic findings on initial CT scans have a high risk of hemorrhage after reestablished blood flow primarily because of the high incidence of reperfusion of irreversibly damaged ischemic tissue. The thrombolytic agent can contribute to hemorrhagic complications (ie, reperfusion of dead tissue), but is not the primary cause. The most effective way to prevent such complications is either to avoid reperfusion of irreversibly damaged tissue or to recanalize the occluded vessel as early as possible. In some patients, the blood flow of the cortex in the distal MCA territory can be rescued by recanalization of the occluded M1 segment with direct angioplasty. Nonetheless, angioplasty alone will not dissolve the clot or reestablish the blood flow effectively, particularly in the perforators, but will further propagate the clot distally. Therefore, the relatively low rates of hemorrhage and clinical recovery suggest that their

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technique of performing angioplasty alone may not be as effective in reestablishing blood flow. If the authors believe that early ischemic findings on the initial CT scan can suggest irreversibly damaged tissue and a high risk of hemorrhage, then early interventional treatment, including PTA, should not be performed in patients who have such findings.

One important question regarding the treatment of acute stroke is whether we are treating reversible ischemia. Our previous reports suggest that reversibility of ischemic tissue can be assessed by SPECT of pretreatment CBF, which can help in the selection of appropriate patients for thrombolysis by reducing hemorrhagic complications and improving outcome (2, 3). Our previous experience also suggests that a combination of thrombolysis and angioplasty is effective in failed thrombolysis cases or reocclusion cases (4). We strongly believe that angioplasty is an effective option in reperfusion therapy for acute ischemic stroke, and can shorten the duration of ischemia and improve the success rate of recanalization. Most importantly, the purpose of angioplasty should be to improve the neurologic symptoms of stroke patients by increasing CBF, not to improve angiographic results.

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### Reply

We appreciate the interest of our colleagues Toshihiro Ueda and William T.C. Yuh regarding our report of direct PTA for MCA occlusion. To our regret, our colleagues have misinterpreted our thesis and results. We reported that four (57%) of seven patients with embolic MCA trunk occlusion showed marked clinical improvement, although all patients had both early ischemic findings on the initial CT scan and LCA involvement, both of which have been reported to be predictive of hemorrhagic complications after thrombolytic therapy (1, 2). This good result indicates that early ischemic findings on the initial CT scan do not always suggest irreversibly damaged tissue.

In patients with these findings, urgent recanalization should be undertaken prior to the onset of irreversible brain damage. In patients with embolic MCA trunk occlusion, the embolus is often so large that it is resistant to thrombolysis. Therefore, mechanical crushing of the embolus by direct PTA is preferred to time-consuming thrombolytic therapy. Our rationale for choosing direct PTA for these patients is based on the high risk of hemorrhagic complication if thrombolytic therapy, using high doses of thrombolytic agents, is performed. We chose direct PTA in order to achieve rapid recanalization, not to avoid using thrombolytic agents. We agree with Ueda and Yuh that angioplasty is an effective option in reperfusion therapy for acute ischemic stroke that can achieve rapid recanalization (3).

In patients with embolic MCA trunk occlusion, conservative treatments often lead to extended space occupying cerebral edema or massive intracerebral hemorrhage owing to late spontaneous recanalization after complete damage of the vessel wall (4). Even if most of the ischemic tissue cannot escape cerebral infarction, therapeutic recanalization might be effective if recanalization could be performed without hemorrhagic complications, and the goal of rehabilitation could be improved. The purpose of recanalization therapy should be to improve clinical outcome, not solely an excellent recovery. We have never aimed to improve angiographic results; we do strive to improve long-term clinical outcome.

In our study, three (43%) of seven patients with embolic MCA occlusion had cerebral infarctions in spite of rapid recanalization, suggesting irreversible ischemic damage. In these three patients, however, neither space occupying cerebral edema nor massive intracerebral hemorrhage was found in the course of treatment because of rapid recanalization

prior to the damage of the vessel wall. Rehabilitation of these three patients went well, and we believe that their clinical outcome was improved by the urgent recanalization therapy.

We have also demonstrated that direct PTA alone could achieve complete recanalization in five (71%) of seven patients with embolic MCA occlusion. Crushed fragments of the embolus migrate distally and often lyse spontaneously, resulting in complete recanalization without thrombolysis. In the other two patients, additional thrombolysis was required because of the distal embolization. Although distal embolization by crushed fragments is a noteworthy problem of direct PTA for cerebral embolism, thrombolysis of these fragments is likely to be easy with small amounts of thrombolytic agents. We agree with Ueda et al that a combination of angioplasty and thrombolysis is effective in some patients. In order to recanalize the occluded vessel as early as possible, direct PTA and subsequent thrombolysis of crushed thrombi should be effective.

Angioplasty is effective in patients with atherothrombotic stroke, particularly in failed thrombolysis or reocclusion cases; however, in patients with atherothrombotic MCA branch occlusion, sufficient arterial patency was not achieved with the minimum dilatation force of 2–3 atm because of the small diameter of the vessel.

In summary, angioplasty is an effective option in reperfusion therapy for acute MCA occlusion, particularly in patients with atherothrombotic stroke. Even in patients with embolic MCA occlusion, when early ischemic findings and LCA involvement are present, urgent recanalization by direct PTA should be performed, and additional thrombolysis may be required in some patients.

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