Acetazolamide Enhancement of HIPDM Brain Flow Distribution Imaging

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Six patients with symptomatic cerebral vascular disease were studied with ^{133}Xe regional cerebral blood flow measurements and HIPDM cerebral imaging after the administration of acetazolamide. The results obtained from this small group suggest this technique may have high sensitivity for detection of cerebral vascular disease.

J Nucl Med 27:1627–1631, 1986

Early identification of individuals with a very high risk of stroke remains an elusive goal. Meyer recently reported application of xenon (Xe) cerebral blood flow (CBF) measurements (Xe-CBF) to an asymptomatic population and found changes in flow in up to 2 years before clinical evidence of cerebral vascular disease (*1*). Radiopharmaceutical chemists have now developed a series of compounds that appear to cross the blood-brain barrier proportionally to blood flow and with radiolabels suitable for single photon emission computed tomographic (SPECT) imaging (*2,3*). *N'N'N'*-trimethyl-*N'*-(2-hydroxy-3-methyl-5-[^{123}I]iodobenzyl-1,3-propanediamine (HIPDM) is one of these agents (*2*). Using a similar agent, Hill described patients in whom cerebral vascular disease or stroke were demonstrated only with these techniques (*4*).

Acetazolamide (diamox), a carbonic anhydrase inhibitor, has been in clinical use for more than 20 years to reduce production of vitreous humor and cerebral spinal fluid and as a diuretic. In addition, by a presently poorly understood action, i.v. administration of acetazolamide produces temporary elevations in cerebral blood flow in normal subjects (*5–8*). Hague reported that the effect on blood flow could be detected within 2 min of injection, with an average maximum response of a 75% increase at ~25 min (*8*). The half-time of the response was 95 min. To confirm this, we studied four patients with other neurologic complaints but without known cerebral or carotid vascular disease with the inhalation ^{133}Xe regional cerebral blood flow (rCBF) technique. The measurements were made at rest and 10 min after acetazolamide (500 mg i.v.) injection. There was a mean hemisphere increase of 32% (range 6 to 53%) in Fl or gray matter flow.

The only published side effects of the drug are very rare transient parathesias (*9*). Vorstrup has used this drug successfully with tomographic Xe-rCBF measurements for evaluation of cerebral vascular disease (*10*).

We wished to use HIPDM to evaluate distribution of rCBF after acetazolamide and to determine if later images would demonstrate any apparent redistribution. The reservoir of intact HIPDM appears to be the lungs but it undergoes degradation to various metabolites in the circulation in animal models (*11*). The same group of investigators have demonstrated that for the first hour in laboratory animals there is a slow influx and efflux of HIPDM from brain tissue but they did not further extend their studies. We wished to increase sensitivity to focal cerebral ischemia. We used Xe-rCBF measurements (by inhalation) to semiquantitate any changes in rCBF found on the acetazolamide-HIPDM studies.

PATIENT STUDIES

We studied six patients utilizing diamox-enhanced HIPDM SPECT imaging for evaluation of cerebral vascular disease (Table 1). Five of the patients had transient ischemic attacks (TIA) with or without a previous cerebral vascular accident (CVA). None had their TIA symptoms at the time of the study. One subject was recovering from a CVA suffered 2 wk previously. When possible the following protocol was used:

1. Resting ^{133}Xe CBF (by inhalation).
2. Intravenous administration of 500 mg acetazolamide.

Received Sept. 9, 1985; revision accepted Jan. 21, 1986.

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TABLE 1
Results of Patients Studied

Patient no.	Symptom or symptoms	CT	Invasive	Diamox and HIPDM (DHIPDM)	Hemisphere rCBF L/R (FI) Pre diamox (ml/100 g/min)	Hemisphere rCBF L/R (FI) Post diamox (ml/100 g/min)	rCBF in area of lesion (L/R) Pre diamox (ml/100 g/min)	rCBF in area of lesion (L/R) Post diamox (ml/100 g/min)
1	TIA	L CVA	LICA occlusion, stenosis RICA by angiography	Left small focal CVA, decrease left hemisphere with normalization except in area of stroke		78/86		75/86
	After left bypass			Even distribution	35/42	39/40	(No lesion)	
2	TIA	Left infarct	Right ICA occlusion, Left ICA stenosis	Decrease R hemisphere virtually normal with resting injection	47/44	56/52	47/40	54/50
	After bypass	Infarct	Frontal infarct at surgery	Fixed frontal normal parietal	36/35	43/39	37/30	43/37
3	TIA	Normal	Normal	Reversible decrease right parietal	58/59	61/61	58/59	63/59
4	TIA	Right infarct	Right ICA occlusion	Focal fixed right parietal	56/51	58/55	59/50	66/54
5	Right hemiplegia	Left infarct	Left ICA occlusion	Left parietal reversible with retention in infarct	59/63	65/73	55/64	58/77
6	TIA	Right capsular infarct	50% Right ICA occlusion	Reversible right anterior parietal	52/57	70/78	44/57	80/69

3. Rest, 10 min.
4. Repeat Xe-CBF.
5. Intravenous administration of ~5 mCi of "hi-purity" iodine-123- (^{123}I) labeled HIPDM.
6. Delay, 10 min.
7. Cerebral SPECT (64 angle, 30 sec/angle) imaging.
8. Additional SPECT imaging at 5–8 hr and 18–24 hr.

We were unable to obtain accurate resting rCBF measurements on one patient.

The Xe-rCBF device was a 32-probe Harshaw instrument interfaced to a DEC PDP 11-04 microcomputer. SPECT imaging was done on a GE 400-AT camera* interfaced to a Computer Design Associates† Nuclear Medicine computer system (DEC VAX 11-750) using CDA supplied software for reconstruction with a Butterworth filter.

One patient (Patient 4) received a second injection of 2.5 mCi of HIPDM 24 hr after the enhanced study while at rest.

RESULTS

All the patients from this very highly selected group had demonstrable abnormalities on the acetazolamide-enhanced SPECT images, some of which were poorly seen with repeat or delayed imaging. Areas of known cerebral infarction did not greatly change in appearance except in one patient. The one patient studied with a second dose of HIPDM had clear abnormalities after diamox which were much less obvious at rest (Fig. 1). We have studied two patients before and after bypass surgery. The enhanced images had equalized in previously decreased areas except in areas of previous or perioperative cerebral infarction (Fig. 2).

The subject studied during the recovery phase of a CVA had a different appearance than the TIA subjects (Fig. 3). The affected hemisphere had marked decrease of HIPDM uptake even outside of the area of computed tomographic demonstrated infarction. By ~20 hr the tracer had accumulated in the area of the infarct while the surrounding and opposite hemisphere brain decreased.

We did not observe the reported marked increases in rCBF except in two patients in this group. Patients 5 and 6 had increases in the apparently normal hemisphere.

Images were obtained over the neck, chest, and abdomen in several subjects at 18 to 20 hr after administration without visualization of the thyroid gland, salivary glands, or stomach. The kidneys were faintly seen. Lung activity had decreased, liver activity had increased, and small amounts of tracer were seen in the small bowel.

DISCUSSION

Presently there are no specific and generally available noninvasive techniques to predict which asymptomatic but "at risk" patients are likely to become symptomatic. Ninety percent of those who have developed TIA symptoms have demonstrable vascular lesions but carotid lesions in asymptomatic patients are not uncommon.

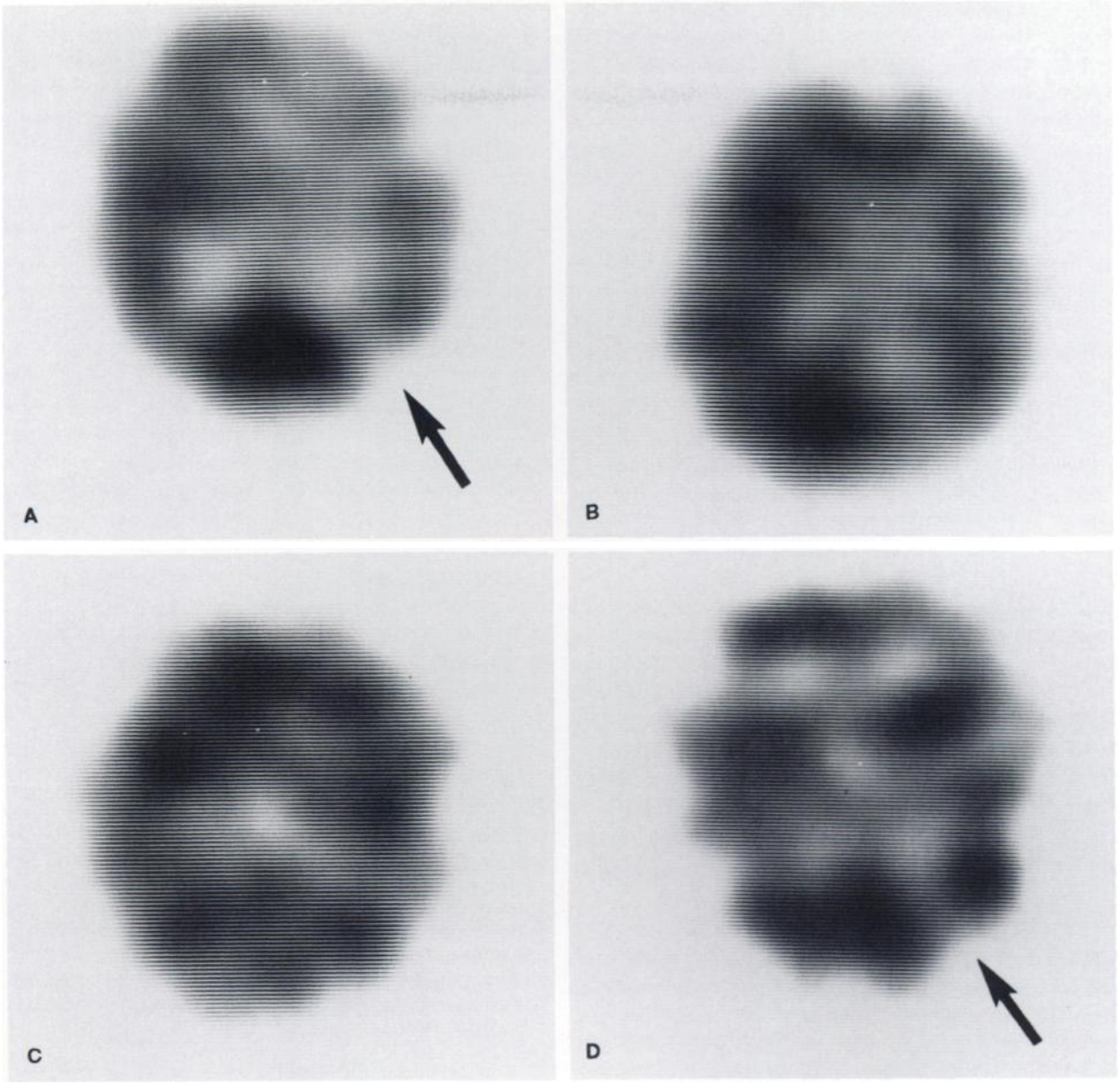

FIGURE 1‡
Patient 1 with left internal carotid occlusion, right internal carotid stenosis, and previous left cerebral infarction. A: Initial acetazolamide-enhanced study prior to bypass surgery showing decreased HIPDM uptake left hemisphere and small left cerebral infarction (arrow). B: Repeat imaging (no additional HIPDM) at 6 hr with some normalization. C: Repeat 20-hr study with almost complete normalization of left hemisphere except in area of infarction. D: Enhanced study 2 mo later after revascularization procedure. Left hemisphere appears normal except for infarct (arrow). Right hemisphere now appears to have less HIPDM uptake than left

Development of practical and specific treatment for patients with very high probability for stroke might depend on sensitive early identification. Our data from six symptomatic patients studied for clinical reasons is preliminary and not a controlled prospective study. We have, however, demonstrated that the enhanced HIPDM study has high sensitivity for detecting cerebral vascular disease with normalization with delayed imaging in some patients with TIA who were asymptomatic at the time of study. The one patient examined with a second administration of HIPDM had images clearly different in appearance from the enhanced study. HIPDM seems to have sufficiently rapid turnover to allow delayed imaging but the physical decay of the label results in degraded images. It is unlikely that the change in appearance over time in some of the TIA patients is from deiodination of the radiopharmaceutical with redistribution of the label. Free iodine should

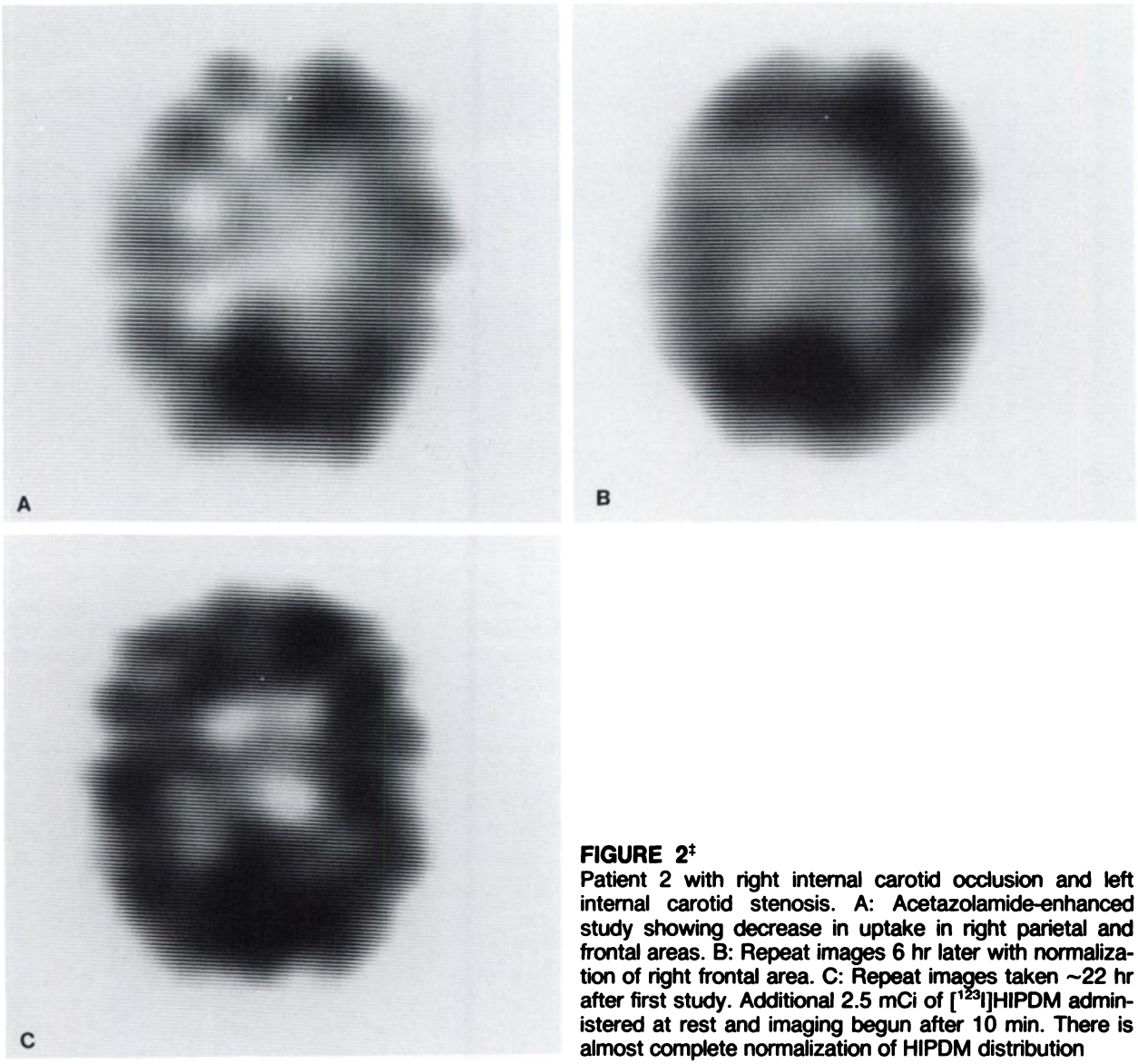

FIGURE 2‡
Patient 2 with right internal carotid occlusion and left internal carotid stenosis. A: Acetazolamide-enhanced study showing decrease in uptake in right parietal and frontal areas. B: Repeat images 6 hr later with normalization of right frontal area. C: Repeat images taken ~22 hr after first study. Additional 2.5 mCi of [^{123}I]HIPDM administered at rest and imaging begun after 10 min. There is almost complete normalization of HIPDM distribution

be cleared through the usual mechanisms and visualized in the target organs.

Delayed images may be "good enough" but the images from the one patient studied with a second dose "at rest" were clearly superior. The cost of HIPDM and especially "hi-purity" ^{123}I makes a second injection difficult to justify.

The one patient with acute CVA demonstrated a different course. We suspect the delayed or retained uptake in the area of the lesion may be from either accumulation of the tracer in the extracellular fluid or from a severe delay in efflux of the tracer from the lesion from severely reduced blood flow.

The relative lack of response to the acetazolamide as measured by the rCBF studies in this group had two likely causes. Many in the group had multivessel cerebral vascular disease. We also chose to time the injection of the HIPDM at ~25 min after the acetazolamide at the time of greatest effect while the rCBF studies were started at 10 min. The 25-min delay is about the same time used for a similar purpose by Vorstrup (*10*).

Recent reports (*12–14*) have shown ^{99m}Tc-labeled radiopharmaceuticals with similar distributions may shortly become available. The use of acetazolamide or similar drugs and cerebral blood flow imaging agents may provide an accurate, safe, simple, and widely available method to screen subjects clearly "at risk" for cerebral vascular disease and stroke.

FOOTNOTES

* General Electric Medical Systems, Milwuakee, WI.

† Siemens Gammasonics (CDA), Des Plaines, IL

‡ All transverse section figures are in TCT format as if the patient is supine and viewed from his feet. All sections are from the approximate same level and orientation.

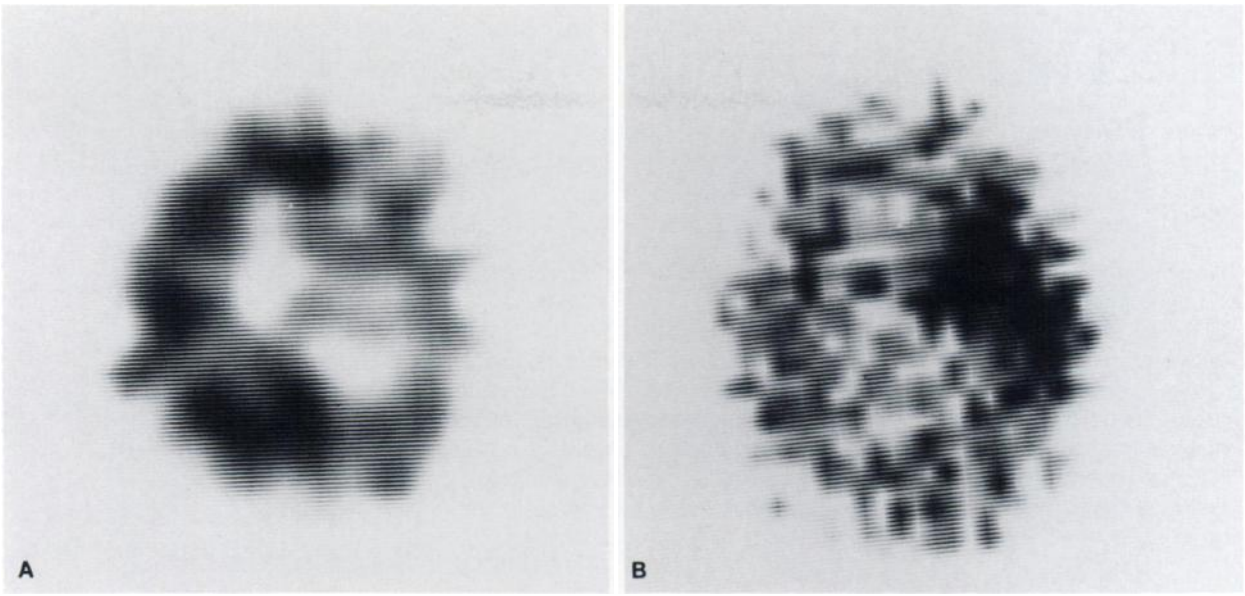

FIGURE 3‡
Patient 5 with left internal carotid occlusion and recent cerebral infarction. A: Initial enhanced study showing decreased HIPDM almost entire left hemisphere. B: 20-hr delayed images with apparent decrease of HIPDM in left and right hemispheres outside of transmission computed tomography demonstrated enhancing infarct area and increased concentration of HIPDM in area of infarct

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