Dynamic SPECT with Xe-133: Regional Cerebral Blood Flow in Patients with Unilateral Cerebrovascular Disease: Concise Communication

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To validate xenon-133 dynamic single photon emission tomography (SPECT) clinically, 74 patients were examined. Strictly unilateral cerebrovascular disease was confirmed in 47 patients by clinical history and by transmission computerized tomography (TCT) and contrast angiography. Twenty-seven were excluded, considered normal. SPECT flow maps were evaluated visually (against TCT) or by automated region of interest (ROI) techniques (12 areas per slice) to measure area flow (AF) (ml/100 g-min) and interhemispherical area flow ratios (AR). These were compared with normal values. Minimum AF in affected hemisphere decreased, and AR-to-normal difference increased, with the severity of the disease. Visually, low-flow areas were detected twice as frequently in SPECT as areas of low density in TCT. In reversible episodes, sensitivity of AF alone was significantly below the sensitivity of combined evaluation of flow and ratio.

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Various methods may be used to map regional cerebral blood flow (rCBF) in man. Inhalation of xenon-133 gas has reached the stage of useful clinical application in the past years. Besides the use of multiple probes, most recently a dynamic single photon emission tomography (SPECT) procedure was introduced by the group of Lassen et al. (*1–4*). First reports deal with computational methods (*2,3*), technical considerations (*4,5*), and preliminary clinical results (*1,5,6–8*).

The present study is aimed at the validation of this SPECT method, using a highly selected group of patients with strictly unilateral cerebrovascular disease (CVD), combined with a clearly defined clinical presentation and a control group for comparison.

MATERIAL AND METHODS

The SPECT instrument and procedure are described in detail elsewhere (*1,4,5*). Using a rapidly orbiting, 64-crystal SPECT scanner* and inhalation of xenon-133 gas (10 mCi/l), measurements of rCBF (ml/100 g-min) were performed in three axial slices. After inhalation for 1 min and exhalation for 3 min, calculation of rCBF was done using specially designed algorithms (*2,3*). During the examination, lights were dimmed and noise was avoided. The patients were asked to keep the eyes closed and to breathe normally. For control, end-tidal pCO_2 was monitored by a capnograph during the examination. Arterial pCO_2 was determined by blood gas analyzer in blood samples taken from the radial artery at the end of the exhalation period. Patients with pCO_2 <33 or >40 mmHg were excluded from the study, since at such levels changed rCBF values due to hyper- or hypoventilation can be expected.

Evaluation of functional images [flow maps, Fig. 1, (left)] was done by introducing 12 regions of interest (areas, ROI) per slice (Fig. 1, (center)). These regions were delineated by a computer program after the observer determined the midline and seven border points on the left hemisphere. The paired ROIs excluded a central band extending 5 pixels (~1.7 cm) on each side of the midline (Fig. 1, center). Each of the half-slices was divided into six areas, A. Since automated evaluation of

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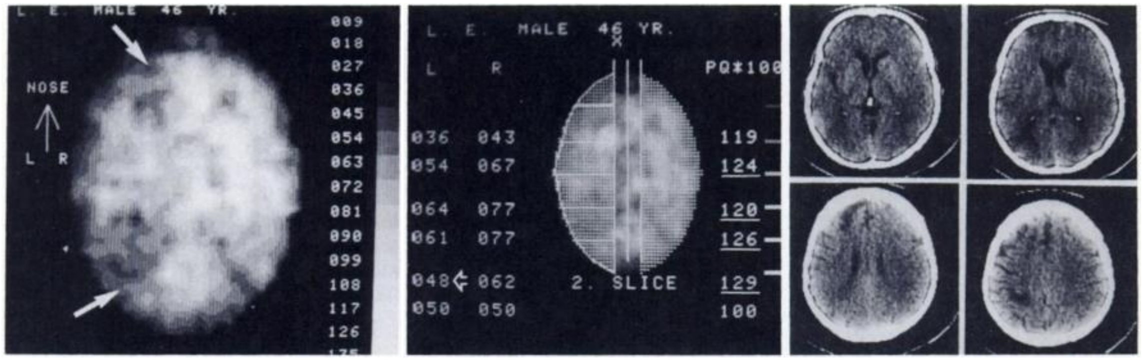

FIG. 1. Six months before examination 46-yr-old male patient developed right-sided PRIND (weakness of right extremities). Radiographic angiography showed occluded left internal carotid artery. SPECT flow map (left, Slice 2) revealed visually low-flow areas within left hemisphere (arrows). With ROI technique (12 areas per slice) only one area (arrow: 48 ml/100 g/min) was below normal (center). However, four (underlined) right-to-left area ratios (PQ = AR) were significantly outside of normal ranges (mean + 2s.d., see Table 2, Slice 2). TCT (right, plain imaging) revealed signs of low perfusion in left hemisphere (widened sylvian fissure, enlarged anterior ventricle) but only two defect areas (frontal and occipito-parietal).

Slice 1 is frequently hampered by Xe-133 uptake in the paranasal sinuses, only Slices 2 [6 cm above the canthomeatal line (CML)] and 3 (10 cm above the CML) were used in the present study.

For each normal subject, the following parameters were calculated from the SPECT data: (a) AF = area flow (ml/100 g-min) in the 24 areas of the two slices; and (b) AR = AF_{right}/AF_{left}, the interhemispheric ratio for flow rates. In the patients, the following were also calculated: (c) ΔAF = difference between the AF on the ischemic side and the lower limit of the comparable normal AF, i.e., (normal AF_{mean} − 2 s.d.) − AF_{isch}; and (d) ΔAR − similarly calculated difference, [normal AR_{mean} − AR_{isch} (Table 1)]. If a patient's affected hemisphere showed one or more area flow values below the mean minus 2 s.d. for the normal group (see "patients") and/or area ratios outside of the mean ± 2 s.d. for normals, he was considered a true positive. The "gold standard" was a combination of positive angiographical and clinical findings pointing to the same hemisphere. Moreover, visual evaluation of slices (flow maps) was used to compare the results with those of other imaging modalities (TCT).

Contrast angiography was performed first, and SPECT and TCT followed within 10 days. In all cases, TCT findings were available from later than 7 days after the attack, but TCT and SPECT studies were no more than a week apart. For visual evaluation and comparison, corresponding TCT slices were subdivided visually into the same 12 areas as in the SPECT Slices 2 and 3, and evaluated for areas of low density typical for CVD.

Biplane radiographic angiography was performed in two projections for both carotid and vertebral arteries, and evaluated by experienced observers. The evaluation included determination of stenosis or occlusion of the common carotid artery, internal carotid artery (ICA), and of the main cerebral arteries (middle = MCA, posterior = PCA) or their branches. The "normal" side was allowed to reveal only slight irregularities but no stenosis >30%. Results of invasive angiography were then used to select the patients, since only patients with unilateral CVD were to be included in the study.

The patient's clinical presentation was used to subdivide the patients into three groups: completed stroke (CS), prolonged reversible ischemic neurological deficit (PRIND = cerebral dysfunction persisting for more than 24 hr after ictus with a tendency to clear), and transient ischemic attack (TIA = focal cerebral dysfunction, completely cleared by 24 hr after onset) (*9,10*). Only the patients with CS had considerable neurological deficits at the time of examination. No patient was studied within the first week after the attack.

Seventy-four patients are included in this study. CVD was excluded in 27 right-handed patients (18 male, 9 female: mean age 45 yr ± 13 s.d.). This group provides

TABLE 1. Xe-133 SPECT: PARAMETER FOR CLINICAL EMPLOYMENT

I	rCBF — absolute values (ml/100 g-min) = flow F	
II	rCBF — relative values (right-to-left ratios) = R	
III	regions of low flow, visually detected	
	1 per pixel (32 × 32)	2 per standard area, A*,
	3 per halfslice	4 individual areas

Combinations used in the present study:

I_2:	area flow AF (compared with normal AF or as differences to lowest normal (mean minus 2 s.d.) area flow = ΔAF)
II_2:	area flow ratio AR (compared with normal AR or as differences to normal mean area flow ratios = ΔAR)
III_2:	visual detected low flow ("defects") (vs areas of low density in TCT)

* 12 areas A per slice.

TABLE 2. Xe-133 SPECT, NORMAL rCBF VALUES FOR AREA FLOW, AF, (ml/100 g-min) AND RIGHT-TO-LEFT RATIOS, AR, IN SLICES 2 AND 3 (ALL DATA MEAN ± s.d.; n = 27)

Slice 2*			Slice 3*		
Left AF	Right AF	AR	Left AF	Right AF	AR
46.6 ± 8.1	49.0 ± 9.6	1.06 ± 0.13	36.0 ± 8.6	37.6 ± 9.4	1.05 ± 0.15
63.7 ± 7.8	66.0 ± 7.6	1.04 ± 0.09	57.4 ± 9.3	57.3 ± 8.2	1.01 ± 0.11
76.7 ± 9.4	76.4 ± 8.3	1.00 ± 0.07	68.9 ± 8.5	70.4 ± 8.0	1.02 ± 0.07
71.3 ± 9.0	69.9 ± 7.5	0.99 ± 0.05	68.1 ± 6.8	68.0 ± 6.8	1.00 ± 0.05
61.4 ± 6.2	60.4 ± 6.5	0.99 ± 0.06	61.8 ± 8.6	61.5 ± 8.8	1.00 ± 0.07
52.9 ± 6.9	51.4 ± 7.1	0.97 ± 0.08	46.2 ± 9.5	46.5 ± 9.1	1.02 ± 0.11

* Top row: frontal, bottom row: occipital.

the "normals." Fifteen patients (aged 52 ± 10 yr) had CS, 16 (aged 49 ± 14 yr) had a history of PRIND, and 16 (aged 58 ± 11 yr) a history of TIA.

RESULTS

Contrast angiography in the group of patients with CS revealed occlusion of the ICA in 11 patients and stenosis of 50% in one patient. Occlusion of the MCA was detected in two patients, and stenosis in one patient. TCT revealed normal findings in three patients and low-density areas in 12 patients.

In the patients with PRIND, contrast angiography revealed occlusion of the ICA in nine patients, stenosis in two, occlusion of the MCA in one, stenosis in two, and stenosis of PCA in two patients. TCT findings were normal in five patients, low-density areas were described in 11 patients.

In patients with TIA, radiographic angiography revealed occlusion of ICA in eight patients, stenosis of >50% in six patients, occlusion of MCA in one, and rarefication of branches of the MCA in one patient. TCT was normal in nine patients, low-density areas were detected in seven.

Table 2 shows the normal rCBF values for the 24 hemispheric areas (12 area flow values for Slice 2, 12 for Slice 3) and normal interhemispherical area-flow ratios. Correlation of mean area flow (mean of 24 flow areas per "normal") and age of the normals revealed a slight decrease of area flow with age (Fig. 2).

Table 3 lists the lowest area flow values found in the affected hemispheres, the corresponding contralateral area flow, the difference between area-flow ratios in patients and normal ratios, and differences between area flow in patients and the lower limit of normal AF (Fig. 1, center). With increasing severity of the clinical history, least area flow decreased and differences between area flow ratios and the normal ratios increased. Contralateral flow values were nearly independent of these relationships.

Significantly low area flow in the affected hemisphere was found in up to 44% of areas (Fig. 1, Table 4). However, in up to 20%, low area flow was detected in the nonaffected side in addition, with no corresponding defects by TCT.

Table 5 illustrates sensitivities derived from evaluation of SPECT by either low area flow values (below normal mean minus 2 s.d.) in the affected hemisphere or by high interhemispherical area ratios (outside normal ranges of 2 s.d., proving a considerable side-to-side difference) or by a combination thereof. The combination gave the highest sensitivities (88–100%). Low area flow values alone were less sensitive (50–80%) (for TIA and PRIND $p < 0.01$).

Visual comparisons between corresponding SPECT and TCT slices of clinically affected hemispheres are summarized in Table 6. Evidently, visual low flow was more frequent in SPECT than defects (low-density areas) in TCT. This was true for all three clinical pre-

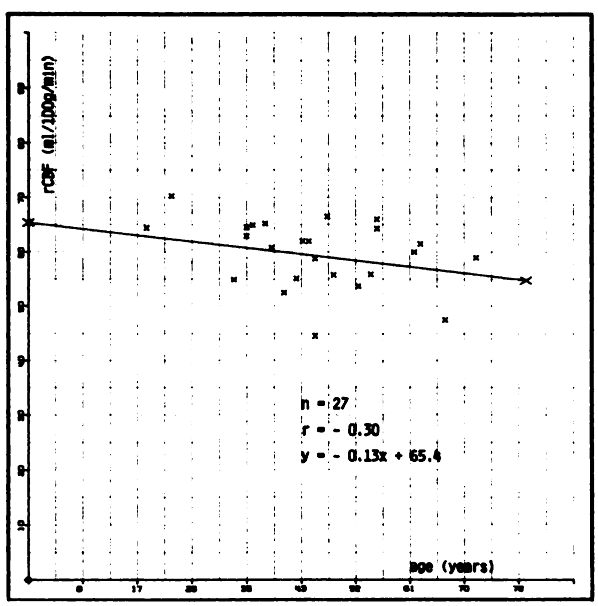

FIG. 2. Age compared with area flow (ml/100g-min as mean of 24 areas per individual) in 27 "normals". Note mild decrease of rCBF with advancing age.

TABLE 3. LOWEST AREA FLOW, AF (AFFECTED SIDE), CORRESPONDING CONTRALATERAL AF, AND DIFFERENCES BETWEEN FLOW AND THE NORM (ΔAF) RATIO BETWEEN FLOW AND NORMAL (ΔAR) IN PATIENTS WITH CS, PRIND, AND TIA

	n	Lowest AF* (ml/100 g-min)		Contralat. AF* (ml/100 g-min)	Δ†AR	ΔAF* (ml/100 g-min)
CS	15	43 ± 17	s‡	60 ± 16	0.39 ± 0.22	14 ± 8
PRIND	16	46 ± 14	s	62 ± 15	0.29 ± 0.14	10 ± 7
TIA	16	50 ± 13	s	60 ± 16	0.20 ± 0.15	8 ± 7

* All values mean ± s.d.
† Δ see Table 1.
‡ s indicates $p < 0.005$ by Student's t-test for paired data.

sentations. In SPECT and in TCT, the number of findings increased with the severity of the disease.

DISCUSSION

Measurement of rCBF has been the goal of many research and clinical studies. Since SPECT systems are involved, there is widespread discussion involving mainly spatial resolution and volume sensitivity (*11*). However, the clinical usefulness of a device or a method does not depend uniquely on these parameters. For instance, computer-assisted radionuclide angiography with Tc-99m DTPA proved to be very effective in detecting patients with cerebrovascular disease by simply using global right-to-left interhemispherical perfusion ratios (*10*). Therefore, we restricted the subdivision of slices into 12 areas each, accepting the relatively low spatial resolution of the system used (>1.7 cm FWHM, Ref. *4*). Thus, with a slice thickness of 2 cm (*1*), areas A cover volumes from 18 cm^3 (frontal and occipital areas) to 36 cm^3 (temporal or parietal areas). This size fits the recommendation of Todd-Pokropek and Jarrit (*12*) that volume elements used for quantitative assessment should be greater than twice the spatial resolution of the system.

For validation purposes we used three methods that we and other authors have found helpful in explaining the patients' clinical presentation or history: absolute flow values (ml/100 g-min) (*1,13*), right-to-left ratios (*1,10,14*), and visually detectable "lesions" in calibrated images (*1,6,7,14*). Moreover, the patients reported here ("normals" or unilateral CVD) were carefully selected by clinical presentation and angiographic findings out of a group of 230 patients examined with Xe-133 SPECT. Large physiological deviations of rCBF values were prevented by monitoring arterial pCO_2 and by keeping the patients at rest during the examination. Moreover, patient's mean ages were close, although this has only minor influence on area flow values (Fig. 2).

With the use of absolute area flow values and area-flow ratios, Xe-133 SPECT correctly determined the involved hemispheres and detected low-flow areas. Furthermore, it discriminated rCBF values in good correlation with the severity (CS, PRIND, TIA) of clinical history (Tables 3, 4). Absolute area flow values alone did not sufficiently separate patients with reversible ischemia from normals (Table 5). Therefore, right-to-left ratios must be used in such patients to obtain clinically useful sensitivities (Tables 3, 5). However, since right-to-left ratios are valid only in unilateral CVD, and since patients with bilateral CVD are common in daily clinical routine, absolute rCBF values are still a desirable discriminator.

Besides mathematical and technical assumptions, and

TABLE 4. QUANTITATIVE (rCBR) EVALUATION OF AFFECTED AND UNAFFECTED HEMISPHERES

Clinical history of:	CS	PRIND	TIA
Number of areas evaluated	180	192	192
affected side	40/90 (44%)	31/96 (32%)	31/96 (32%)
Numbers of areas with low AF in one slice*			
unaffected side	18/90 (20%)	8/96 (8%)	19/96 (20%)

* Per patient. Side selected by clinical presentation and angiographic findings, and slice by lowest area flow (AF) value. Each patient presents 12 areas.

TABLE 5. NUMBER OF PATIENTS WITH TRUE POSITIVE LOW AREA FLOW (AF) (AFFECTED SIDE), AREA RATIO (AR) OUTSIDE NORMAL LIMITS, OR A COMBINATION THEREOF

Clinical history of	CS	PRIND	TIA
Low AF*	12/15	9/16	8/16
Sensitivity	80%	56%†	50%†
AR ≶ mean ± 2s.d.	13/15	15/16	14/16
Sensitivity	87%	94‡	88%‡
Combination	14/15	16/16	14/16
Sensitivity	93%	100%	88%

* Below "normal" mean minus 2 s.d.
† VS ± $p < 0.01$.

compromises inherent in the xenon-133 procedure, described by others in detail (*5,9,15,16*), the physiological variation of rCBF in man may play a role by blurring exact limits of normal values (established as mean minus 2 s.d. for "normals"). Moreover, in the present study, with TIA and PRIND patients long after the attack, mean interhemispherical differences of area flow were not higher than 16 ml/100 g-min and divergence from the ipsilateral normal flow limit was only 10 ml/100 g-min (Table 3). Likewise Gibbs et al. (*13*), working with asymptomatic patients with unilateral carotid occlusion, found reduction of hemispherical cortical flow below the contralateral of 7 ml/100 g-min, and of 6 ml/100 g-min compared with normal individuals. Therefore, these relatively small changes of flow are an additional limiting factor in detecting such patients.

TCT, a method for excellent structural presentation, showed significantly less abnormality as regards the number of low-flow areas (Fig. 1), in all three groups of patients (Table 6). This finding confirms the results of other groups (*14,17,18*) showing that in CVD areas of depressed regional flow or metabolism are greater than areas of low density in TCT. Moreover, areas of low flow occurred in nonaffected hemispheres (Table 4) without structural or angiographical correlations. These findings can reflect "false positives." However, they may also be related to persisting focal contralateral flow defects, experienced in patients with acute insults (*19*).

We conclude that xenon-133 SPECT is a useful tool for the noninvasive determination of rCBF and related ratios in patients with unilateral CVD. If the clinical presentation was completed stroke or PRIND, the sensitivity was greater than 90%. In TIA, it was 88%. The use of absolute flow values alone revealed low area flow only in about 50% of patients with reversible ischemic deficits. However, since in occlusive carotid disease a fall of CBF is considered to be the second step of the response after increase of cerebral blood volume (*13*), normal rCBF values in such patients may reflect the individual severity of the disease.

FOOTNOTE

* Tomomatic 64, Medimatic, Copenhagen, Denmark.

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TABLE 6. COMPARATIVE RESULTS OF VISUAL EVALUATION OF ONE SPECT SLICE AND CORRESPONDING TCT*

Clinical history of:	CS	PRIND	TIA	Total
Number of areas (100%)	180	192	192	484
VLF* in SPECT	61 (34%)	53 (28%)	23 (28%)	24%
	s†	s†	s†	
Defect in TCT	36 (20%)	25 (13%)	10 (5%)	
13%				

* Visually detected low-flow regions (VLF) compared with zones of low density (defect) in TCT.
† s indicates $p < 0.025$.

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