Cerebral Postischemic Hyperperfusion Assessed by Xenon-133 SPECT

Yves R. Tran Dinh, Olivier Ille, Jean-Pierre Guichard, Michel Haguenau and Jacques Seylaz

Departments of Functional Nervous System Imaging, Neurology and Neuroradiology, Hôpital Lariboisière, Paris; Cerebrovascular Research Laboratory, CNRS UA 641, I.F.R Circulation-Lariboisière, Faculté de Médecine Lariboisière-Saint Louis, Université Paris VII, Paris; Department of Medicine, Hôpital de Mantes, Mantes la Jolie, France

In this study, the functional and clinical evolution of the cerebral postischemic hyperperfusion (CPH) were evaluated. **Methods:** Forty-four noncomatose patients suffering from unilateral cerebral ischemia located in the internal carotid territories were studied. Twenty-five consecutive patients having CPH with ^{133}Xe-SPECT cerebral blood flow (CBF) measurement and 19 patients without cerebral hyperperfusion matched for age. CBF, vasoreactivity to acetazolamide and the evolution of the clinical state, scored by the National Institutes of Health scale for stroke, were compared. **Results:** CPH coincided with CT-scan abnormalities in 57% of cases. The mean cerebral vasoreactivity to acetazolamide was comparable in the two groups, but there was local vasoplegia in the hyperperfused areas in 20% of CPH patients, including two cases (8%) with a steal syndrome. Comparison of the initial and late clinical scores showed no significant difference between patients with and without CPH. For patients without CPH, the interhemispheric CBF asymmetry was correlated with the initial and the late scores (p < 0.0001, r = 0.81). For the CPH group, the interhemispheric asymmetry, compensated or even inverted by the hyperperfusion, was not correlated with the initial score (ns, p = 0.051, r = 0.42) and was weakly correlated to the late score (p = 0.048, r = 0.43). **Conclusion:** The cerebral hemodynamics remain normal in 80% of cases of CPH patients. The presence of CPH does not interfere with the clinical evolution. The initial and late clinical scores were not different compared to those of patients without hyperperfusion. The clinical outcome of the CPH patients cannot be accurately predicted by the interhemispheric asymmetry.

Key Words: xenon-133; SPECT; cerebral blood flow; cerebral postischemic hyperperfusion

J Nucl Med 1997; 38:602–607

Normal brain function requires adequate amounts of arterial glucose and oxygen supplied by the cerebral circulation. In case of dramatic decrease in cerebral blood flow (CBF), the survival of the neurons depends on a minimal blood perfusion threshold, below which a deficit in neural function occurs resulting in irreversible cellular damage if the ischemia lasts sufficiently (*1*). Reperfusion after ischemia may lead to a transient hyperperfusion state in which the regional CBF is increased above the normal level. This vascular event is accompanied by low metabolism in the hyperemic areas (*2*) and has been called "luxury perfusion" (*3*) or cerebral postischemic hyperperfusion (CPH). Despite a local perfusion level clearly above the ischemic threshold, CPH is considered by many to be a phenomenon which may interfere with clinical recovery (*4*). These controversial notions led us to examine a group of consecutive patients for the temporal and functional characteristics of CPH and its vasoreactivity to acetazolamide, assessed by ^{133}Xe-SPECT measurements of CBF. The clinical evolution

of the CPH patients was compared to that of a group consisting of ischemic-stroke patients without hyperperfusion.

MATERIALS AND METHODS

Patients

A total of 44 patients underwent ^{133}Xe-SPECT measurement of CBF at the acute or subacute phase of unilateral cerebral ischemia located in the internal carotid artery territories. The indication for the SPECT examination was the assessment of the cerebral vasoreactivity with the acetazolamide test. Two groups were constituted based on whether or not they showed CPH with ^{133}Xe-SPECT. There were 25 consecutive patients showing focal CPH by ^{133}Xe-SPECT: 21 ischemic strokes and 4 transitory ischemic attacks (TIA) (14 men, 11 women; mean age 58.1 yr; range 23–87). The CBF data of the CPH group was compared to those of the other 19 patients without cerebral hyperperfusion, matched for age (13 men, 6 women; mean age 59.6 ± 3.7 yr). The patients without CPH underwent the CBF measurement within the same time range after the clinical onset. In addition, all the patients had CT scan and ultrasonic examination (cervical Doppler, echotomography and transcranial Doppler when a temporal window was present). Some of them underwent angiography (patients with CPH = 8, patients without CPH = 8). Excluded from the study were comatose stroke patients, because the increase in the intracranial pressure by acetazolamide injection may aggravate the ischemic brain swelling, and also patients with either head trauma or intracerebral or subarachnoid hemorrhage.

Clinical Scoring

The neurological clinical evolution was assessed by clinical examination and scored using the National Institutes of Health stroke scale (NIH), which expresses the severity of neurological impairment from 0 (normal) to 42 (*5*). The NIH scale was scored on entry (NIH1) and after 1-mo evolution (NIH2).

CBF Measurement

Quantitative CBF was measured using a dedicated SPECT camera and the intravenous ^{133}Xe method. Details of the procedure and calculations are described elsewhere (*6–8*). CBF values are expressed as ml · 100 g^{-1} · min^{-1}. The cerebral vasoreactivity was assessed after intravenous injection of acetazolamide (Diamox, 1000 mg) given after a 30-min resting state. The second SPECT measurement was made 20 min after this injection. Three 20-mm-thick slices, located 10, 50 and 90 mm above the orbitomeatal line (OM), were scanned. A computer program (head-independent region of interest software) was used to make automatic adjustments for the size of each brain and to obtain flow values for each vascular territory and symmetry. The presence of the hyperperfused area located in the hemisphere responsible for clinical deficit was first analyzed visually, then outlined manually. The regional perfusion of areas that were 7% or greater than its normal symmetrical value was defined as CPH. This percentage was found to be the threshold of significant regional interhemispheric

asymmetry in normal subjects in our laboratory (8). The hemispheric mean of either slice 2 (OM + 50 mm) or slice 3 (OM + 90 mm), where CPH was maximal, was chosen for statistical analysis. The data were analyzed using simple correlation by the least squares method and Student's unpaired t-test. Values, expressed as means ± s.e.m., were considered to be significantly different when $p < 0.05$.

RESULTS

The characteristics of all the patients are summarized in Table 1. The CPH patients and those without CPH were sampled from a larger population studied with the ^{133}Xe technique, and the proportion of the different pathologies responsible for the cerebral ischemia was found to be similar for each group.

The time between the onset of the symptom and quantitative SPECT ranged from 1 to 15 days with a mean of 5.6 ± 0.5 days for the CPH patients and 6.1 ± 0.6 for the patients without CPH (ns). The majority of the patients in the two groups was under treatment with anticoagulants when CBF was measured (patients with CPH = 14; patients without CPH = 15). This treatment was started as soon as possible, after having excluded the possibility of a hemorrhagic infarct, generally at hospitalization.

The location of the CPH and the CT scan abnormalities are given in Table 1. The four TIA patients had normal CT scans. The hyperperfused areas were superimposed partially or totally over the CT scan hypodensity in 12 patients (57%), while the hyperperfusion area did not coincide with the CT-scan abnomalies in the nine remaining patients. CPH was associated with a CT-scan cerebral mass effect only in one case (Patient 7), whereas there were three swollen brains in the group of patients without CPH (Patients 31, 38 and 39).

Angiography was performed at 11.0 ± 2.2 days after the clinical onset, in eight CPH and eight patients without CPH. The eight CPH patients included four with total reperfusion (two with angiographic blushes suggesting "luxury perfusion", Patients 6 and 13) and persistent parietal defects in the four others. Functional anastomoses were found from cortical collaterals (50%) and/or from the circle of Willis (anterior and/or posterior communicating arteries, 87%) and/or from the ophthalmic artery (12%) in the CPH group. The percent was similar for the group without CPH (see Table 1).

The vasodilation induced by Diamox had a similar amplitude in the two groups (CPH group-ipsilateral side to ischemia 37% ± 4%, contralateral side 46% ± 4%; group without CPH-37% ± 4% and 45% ± 5%, respectively). Most of the patients responded normally to Diamox. In the CPH patients, the induced vasodilation, including the hyperperfused areas, was normal in 14 cases (56%). There was no regional vasoreactivity in the hyperemic area in five cases (20%), including two cases of intracerebral steal syndrome (Patients 15 and 16).

The mean initial clinical scores (NIH1) for each group were compared to determine whether the clinical state of the CPH group was worse than that of the group of patients without CPH. The TIA patients (n = 4) were excluded from the CPH group when testing the clinical score. There was no significant difference between the CPH and the group of patients without CPH, although the score of the first group was slightly higher (see Table 2). The 1-mo clinical scores (NIH2) were then compared to determine whether the presence of CPH had improved the clinical outcome. There was no significant difference (see Table 2). The evolution of the NIH scores is shown in Figure 1.

The mean interhemispheric asymmetry (mean contralateral-

ipsilateral CBF to the ischemic stroke) was significantly greater in the group without CPH (3.73 ± 0.88 ml · 100 g^{-1} · min^{-1}) than in the CPH group (−0.66 ± 0.55; $p < 0.0001$) because of the presence of the hyperemic area. This led to a highly significant correlation between the clinical scores and the interhemispheric asymmetry for the group without CPH, whereas there was zero (for NIH1) or poor (for NIH2) correlation for the CPH group (see Table 3). Diamox-induced cerebral vasodilation did not significantly change these correlations.

DISCUSSION

Prior to the discussion, two comments concerning the results should be made: First, these results were obtained in a selected population in which the measurement of CBF was motivated by the study of the cerebral hemodynamics and from which patients in a precarious clinical state or comatose, where the acetazolamide injection could have aggravated the intracranial pressure, were excluded. This explains why there were no deceased patients in either of the two groups and why the clinical scores were probably underestimated. Second, the association of most of the CPHs with an area of hypoperfusion and with intrahemispheric diaschisis probably blunts the statistical significance.

It is generally agreed that cerebral CPH results from reperfusion, but the use of this term can lead to ambiguity. In experimental conditions, the re-establishment of blood flow after total cerebral ischemia provokes a brutal biphasic response, an initial CPH followed by a more or less severe drop in CBF (9–11). Experimental reactive CPH is probably due to the metabolic overshoots produced by ischemia, but reperfusion also alters the production of endothelial vasoactive factors (12–14). CPH seems to be a prerequisite for a favorable outcome in experimental ischemia-reperfusion (15).

Pathological CPH observed in humans is different from experimental reactive CPH because it often occurs many hours or days after the onset of ischemia and lasts longer. It results from a longer duration of ischemia, and the metabolic consequences with release of vasodilator metabolites is more important. Nevertheless, the occurrence of acute reactive CPH as well as the following hypoperfusion phase as seen in animal experiments cannot be absolutely excluded in humans.

The time separating the onset of ischemia and the beginning of the pathological CPH depends on arterial recanalization or setting of the collateral circulation. Our observation of hyperemia with ^{133}Xe-SPECT, about 6 days after stroke, points to partial or complete spontaneous thrombolysis. Within the first 6 hr on stroke patients with angiographically verified occluded arteries, Ueda et al., using ^{99m}Tc-labeled hexamethylpropyleneamine oxime, reported no case of CPH (16). Comparison of therapeutically induced arterial reopening and spontaneous reperfusion in ischemic strokes showed that reperfusion was common but usually partial during the first 48 hr (17). Nevertheless, CPH seems to occur rarely within the first 6 hr. In that interval, Guibilei et al., in 32 stroke patients, found only one case of CPH (3%) (18). There were four other cases (12%) 1 wk later. Shimogesawa et al., in 31 patients, found 10% of focal hyperperfusion within this period (19). In the same way, late hyperperfusion has been observed many weeks after the onset of cerebral ischemia (20). These late hyperperfusions probably differ from the early hyperemias by distinct physiological characteristics such as the involvement of nonendothelial nitric oxide (NO) (21,22). The real duration of CPH may be days or weeks. In our study, five patients had a second CBF measurement (4–9 days after the first SPECT), and the hyperperfusion

TABLE 1
Characteristics of Postischemic Hyperperfusion Group and Patients Without Hyperperfusion (Control)

Patient no.	Age (yr)	Sex	Interval between onset and SPECT (days)	NIH stroke scale NIH1 (initial)	NIH2 (1 mo)	Clinical diagnosis	Angiography	Coincidence of SPECT hyperperfusion and CT scan hypodensity	Local vasoreactivity of the postischemic hyperperfused area
CPH									
1	76	M	7	14	6	L ICA occlusion	nd	Partial (ant MCA)	Absence
2	70	M	7	10	8	Cardioembolic	nd	No	Normal
3	60	F	3	6	1	R ICA occlusion	nd	No	Normal
4	48	M	6	4	0	R ICA dissection	No reperfusion, parietal defect, AC+	No	Normal
5	56	F	6	14	5	Undetermined	nd	Complete	Normal
6	32	F	6	14	7	Undetermined	Recanalization, blush	Partial (ant MCA)	Absence
7	65	M	5	17	14	R ICA occlusion	nd	Partial (ant MCA)	Normal
8	65	M	5	7	3	L ICA occlusion	nd	No	Decreased
9	76	F	4	15	4	Cardioembolic	nd	Partial (post MCA)	Normal
10	80	F	1	2	0	Cardioembolic	nd	No	Normal
11	44	M	5	2	0	R ICA occlusion	No reperfusion, parietal defect, AC+, PC+, Cort+	Complete	Decreased
12	52	M	6	6	3	R ICA dissection	Recanalization, AC+, PC+, Oph+, Cort+	Partial (post MCA)	Decreased
13	35	M	5	30	17	L ICA dissection	Recanalization, AC+, Cort+, blush	Partial (ant MCA)	Normal
14	42	M	6	8	4	R ICA embolism	No reperfusion, parietal defect, AC+, PC+, Cort+	No	Decreased
15	71	F	3	10	1	Undetermined	nd	No	Absence + steal
16	47	F	6	20	14	Bilateral carotid dissection	Recanalization, AC+, PC+	No	Absence + steal
17	78	M	5	6	4	R ICA embolism	nd	Partial (ACA)	Normal
18	87	F	8	11	6	L intracavernous ICA occlusion	nd	No	Normal
19	52	F	8	22	10	R ICA dissection	No reperfusion, parietal defect, AC+, PC+	Partial (post MCA)	Absence
20	68	M	10	21	18	L ICA occlusion	nd	Complete	Decreased
21	54	M	15	23	19	R ICA dissection	nd	Partial (ant MCA)	Decreased
22	45	M	5			L ICA embolism (TIA)	nd	Normal CT scan	Normal
23	23	F	2			Undetermined (TIA)	nd	Normal CT scan	Normal
24	67	M	4			L ICA embolism (TIA)	nd	Normal CT scan	Normal
25	61	F	2			Antiphospholipid syndrome (TIA)	nd	Normal CT scan	Normal
Control patients									
26	40	F	4	1	0	R ICA dissection	nd	–	–
27	33	M	8	10	3	L ICA dissection	No defect, AC+, PC+	–	–
28	70	M	8	4	1	R ICA embolism	No defect, AC?, PC+	–	–
29	68	M	4	5	1	Hemodynamic	Parietal defect, AC+, PC+	–	–
30	85	F	8	7	6	L ICA embolism	nd	–	–
31	47	M	6	13	9	R ICA occlusion	nd	–	–
32	50	F	4	17	8	L ICA dissection	No defect, PC+	–	–
33	58	M	1	2	1	Hemodynamic	No defect, AC−, PC−, Oph+	–	–
34	87	M	6	7	6	Cardiac embolism	nd	–	–
35	78	M	9	7	3	L ICA embolism	No defect, AC−, PC−	–	–
36	39	M	4	20	13	L ICA dissection	nd	–	–
37	64	M	5	7	3	Undetermined	nd	–	–
38	65	M	4	22	17	R ICA embolism	nd	–	–
39	63	F	7	12	6	R ICA embolism	nd	–	–
40	64	F	12	18	12	L ICA occlusion	nd	–	–
41	40	M	4	8	0	Antiphospholipid syndrome	Local defect, AC?, PC+	–	–
42	75	F	9	7	6	R ICA occlusion	nd	–	–
43	69	M	8	3	2	Cardioembolic	nd	–	–
44	38	M	4	13	6	R ICA dissection	No defect, AC+, PC+	–	–

CPH = cerebral postischemic-hyperperfusion group; NIH1 = initial clinical score; NIH2 = 1-mo clinical score; ICA = internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery; AC = anterior communicating artery; PC = posterior communicating artery; Oph = ophtalmic artery; R = right side; L = left side; TIA = transitory ischemic accident; + or − = presence or absence of collateral circulation; nd = not done.

TABLE 2
Initial (NIH1) and 1-mo (NIH2) Clinical Scores for Postischemic Hyperperfusion and Patients Without Hyperperfusion (Control)

| | Group | | |
	CPH	Control	p
NIH1	12.5 ± 1.6	9.6 ± 1.3	0.20 (ns)
NIH2	6.9 ± 1.3	5.4 ± 1.1	0.41 (ns)

NIH = National Institutes of Health.

TABLE 3
Correlation Between Interhemispheric Asymmetry and Clinical Scores Before and After Vasodilation Induced by Acetazolamide (Diamox)

| | Interhemispheric asymmetry | | | |
| | CPH | | Control | |
	p	r	p	r
Basal state				
NIH1	0.051 (ns)	0.42	<0.0001	0.81
NIH2	0.048	0.43	<0.001	0.81
After Diamox				
NIH1	0.108 (ns)	0.36	<0.001	0.69
NIH2	0.404 (ns)	0.19	<0.001	0.75

CPH = cerebral postischemic-hyperperfusion group; control = patients without cerebral hyperperfusion; NIH1 = initial clinical score; NIH2 = after 1 mo.

was not seen at the second examination in four cases (see illustrative case, Fig. 2).

Three inter-related hemodynamic consequences of focal cerebral ischemia may influence the clinical outcome: First, there is the ischemic penumbra surrounding the infarction in the acute phase (23). In our study, there were four cases of TIA in which the CPH was located in the zone that may well correspond to the ischemic penumbra restored to normal by reperfusion. This unexpected finding shows that a brief ischemic event is able to induce CPH extending for many days. In the same way, most of the CPH areas (57%) were located close to the ischemic zone. The remote postischemic hyperemia in the remaining CPH patients may be due to the migration of an embolus (24), which caused reperfusion in one territory and persistent ischemia in a neighboring one. Second is the vasomotor paralysis, responsible for loss of autoregulation in the acute stage of strokes (25). CPH may be responsible for a steal phenomenon that aggravates the hypoperfusion of the bordering regions. In our study, vasoparalysis occurred in only five cases (20%), including two cases of

intracerebral steal syndrome (8%). Normal responses in the remaining 80% of patients leads us to hypothesize that the arterioles in the CPH region and in the developing infarct were not grossly abnormal. Third, there is the reperfusion which seems to be a necessary condition for improvement of the clinical outcome (26–28). When the arterial obstruction persists, the border zones or watershed areas may be reperfused through the leptomeningeal anastomoses.

Apart from cerebral ischemia, hyperperfusion can also have many other causes. Associated with head trauma, it generally has a bad prognosis because it aggravates brain swelling and increases intracranial pressure (3,29,30). Some workers have expressed the same reservations about ischemic strokes (4,31). In our selected population, we did not find any evidence of "stroke in progression," which might have been found if gross edema or hemorrhagic transformation of the infarct had occurred during reperfusion. Other studies suggest that early CPH after ischemic stroke has an excellent clinical outcome (18). Our results, in contrast, agree with those of Heiss et al. (PET study) who showed no prognostic difference between strokes with and without postischemic hyperemia (32) and those of Limburg et al. who studied patients with late SPECT hyperfixation (33). Some investigators have used nonquantitative SPECT as a tool to predict the clinical outcome of ischemic strokes. They showed that the hypoperfusion was strongly correlated with the outcome if the examination was performed less than 72 hr after symptom onset (18,33–36). Our results confirm that for patients without CPH, the interhemispheric asymmetry was proportional to the severity of the initial neurological deficit (NIH1) and may predict the outcome (NIH2). Beyond the first week, CPH became more frequent and decreased the interhemispheric asymmetry leading to a poor correlation between the hypoperfusion and the outcome (35).

Contrasting with animal models, which indicate that the optimum time for drug therapies is at 4–8 hr after the onset of ischemia, studies using thrombolytic therapy show that some clinical improvement may be obtained after this period (17). This calls into question the beneficial effect of cerebral postischemic hyperperfusion, which generally occurs far later, when the fate of the tissue is theoretically settled. If available in a stroke unit, the ^{133}Xe-CBF measurement is of little value for determining the prognosis in the subacute phase, but is certainly of value to justify thrombolytic therapy during the first few hours.
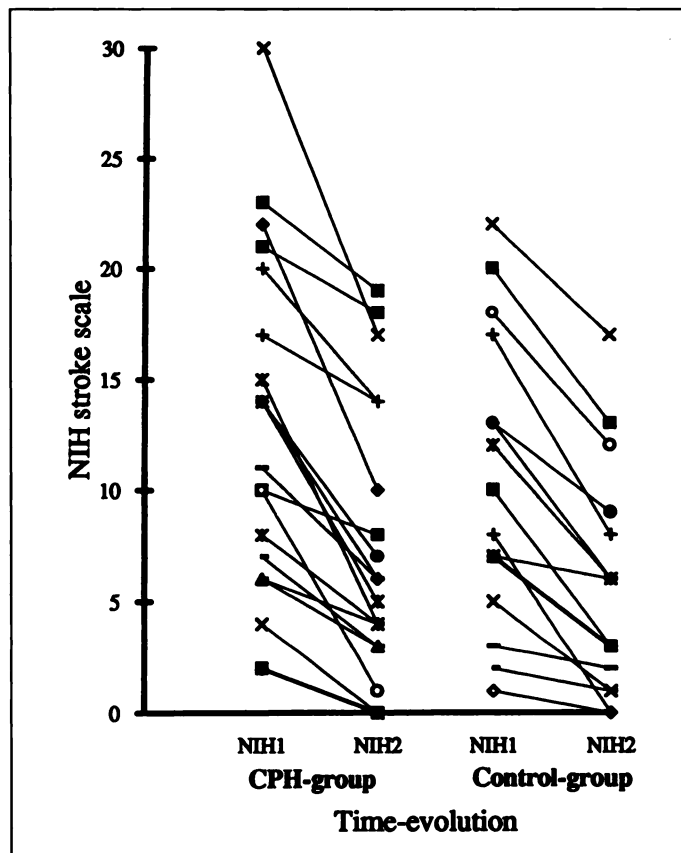

FIGURE 1. Changes in the neurological scores for the CPH and the control patients. The mean values of the NIH1 scores were 12.5 ± 1.6 for the CPH patients and 9.6 ± 1.3 for the control patients (not significantly different, p = 0.20). The NIH2 scores were 6.9 ± 1.3 for the CPH patients and 5.4 ± 1.1 for the control patients (not significantly different, p = 0.41).
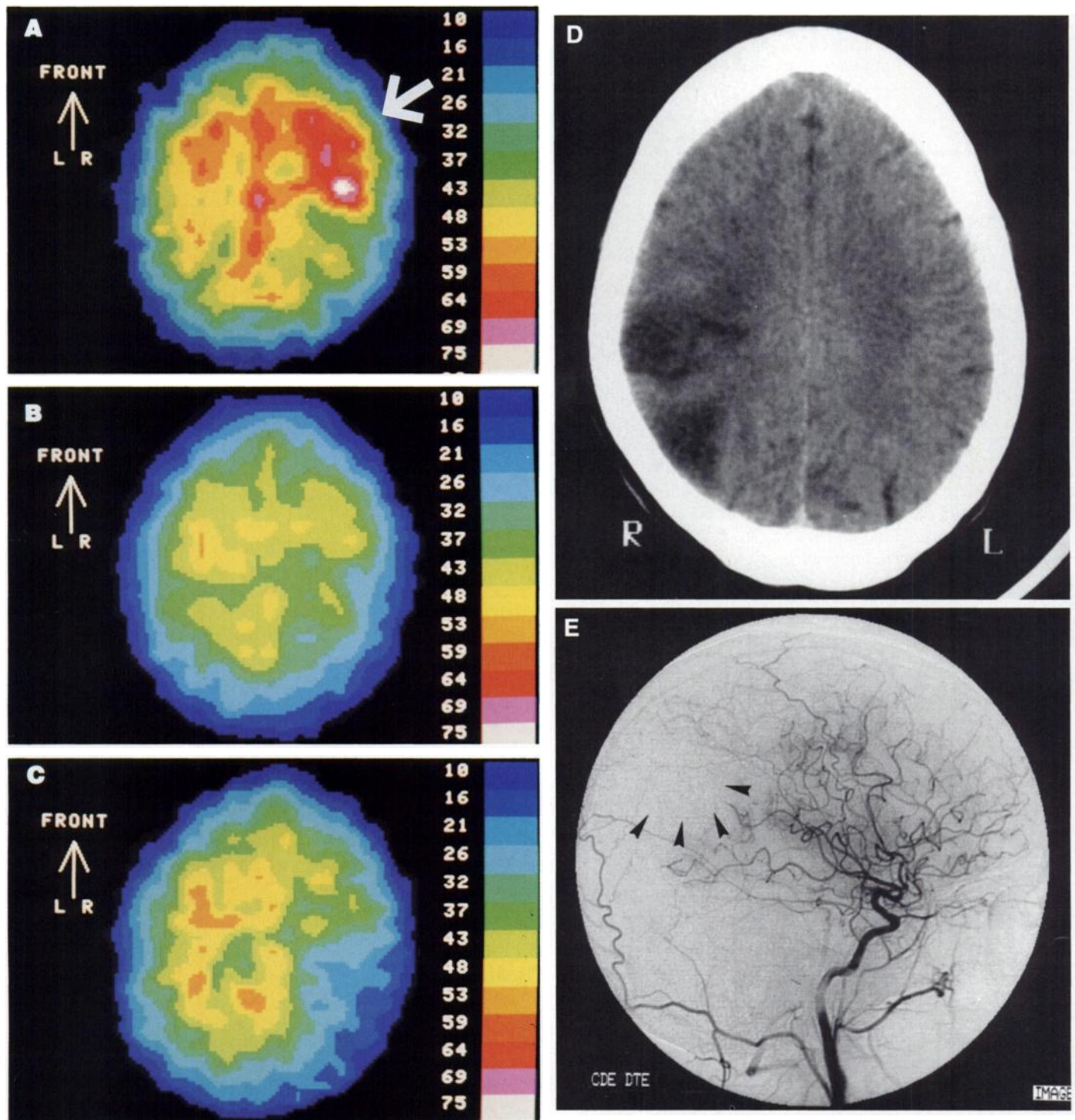
FIGURE 2. CPH assessed by quantitative ^{133}Xe-SPECT. Patient 14 (male, 42 yr) was hospitalized 3 days after the onset of brutal left hemiparesia due to a right internal carotid artery embolism. His initial clinical NIH1 score was 8. CT scan (day 3 after onset) shows right parietal hypodensity (D). (A) The first SPECT (Day 6) shows CPH located in the superior right frontorolandic region (arrow) neighboring a discreet right parietal hypoperfused area that matched the CT-scan abnormalities. The vasoreactivity of the CPH region to acetazolamide was slightly lower (+25%) than that of the contralateral region (+32%). (E) Angiography (Day 13) shows a persistent right temporoparietal defect (arrows) and functional right anterior and posterior communicating arteries as well as cortical anastomoses. (B) The second SPECT (Day 15) shows the arrest of CPH and a slight increase in the right parietal hypoperfusion. The 1-mo clinical score NIH2 was four. (C) The third SPECT (Day 82) shows that perfusion of the initial CPH region was almost normal, while considerable hypoperfusion remained on the right parietal region. All the CBF-SPECT have the same color scale.

REFERENCES

1. Astrup J, Symon L, Siesjö BK. Thresholds in cerebral ischemia—the ischemic penumbra. *Stroke* 1981;12:723–725.
2. Baron JC, Rougemont D, Soussaline F, et al. Local interrelationships of cerebral oxygen comsumption and glucose utilization in normal subjects and in ischemic stroke patients: a positron tomography study. *J Cereb Blood Flow Metab* 1984;4:140–149.
3. Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. *Lancet* 1966;2:1113–1115.
4. Skyhøj Olesen T, Larsen B, Bech Skriver E, Herning M, Enevoldsen E, Lassen NA. Focal cerebral hyperemia in acute stroke. Incidence, pathophysiology and clinical significance. *Stroke* 1981;12:598–606.
5. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20:864–870.
6. Stokely EM, Sveindottir E, Lassen NA, Rommer PA. Single photon dynamic

computer-assisted tomograph for imaging brain function in multiple cross sections. *J Comput Assist Tomogr* 1980;4:230–240.

7. Celsis P, Goldman T, Henriksen L, Lassen NA. A method for calculating regional blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 1981;5:641–645.

8. Tran Dinh YR, Mamo H, Cervoni J, Caulin C, Saimot AG. Disturbances in the cerebral perfusion of human immune deficiency virus-1 seropositive asymptomatic subjects: a quantitative tomography study of 18 cases. *J Nucl Med* 1990;31:1601–1607.

9. Todd NV, Picozzi P, Crockard HA, Ross RR. Reperfusion after cerebral ischemia: influence of duration of ischemia. *Stroke* 1986;17:460–466.

10. Traupe H, Kruse E, Heiss WD. Reperfusion of focal ischemia of varying duration: postischemic hyper- and hypoperfusion. *Stroke* 1982;13:615–622.

11. Macfarlane R, Tasdemiroglu E, Moskowitz MA, Uemura Y, Wei EP, Kontos HA. Chronic trigeminal ganglionectomy or topical capsaicin application to pial vessels attenuates postocclusive cortical hyperemia but does not influence postischemic hypoperfusion. *J Cereb Blood Flow Metab* 1991;11:261–271.

12. Hempel SL, Haycraft DL, Hoak JC, Spector AA. Reduced prostacyclin formation after reoxygenation of anoxic endothelium. *Am J Physiol* 1990;259:C738–C745.

13. Lefer AM, Lefer DJ. Pharmacology of the endothelium in ischemia-reperfusion and circulatory shock. *Annu Rev Pharmacol Toxicol* 1993;33:71–90.

14. Summers ST, Zinner MJ, Freischlag JA. Production of endothelium-derived relaxing factor is compromised after ischemia and reperfusion. *Am J Surg* 1993;166:216–220.

15. Miller CL, Lampard DG, Alexander K, Brown WA. Local cerebral blood flow following transient cerebral ischemia. I. Onset of impaired reperfusion within the first hour following global ischemia. *Stroke* 1980;11:534–541.

16. Ueda T, Hatakeyama T, Kumon Y, Sakaki S, Uraoka T. Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT. *Stroke* 1994;25:298–303.

17. Baird AE, Donnan GA, Austin MC, Fitt GJ, Davis SM, McKay WJ. Reperfusion after thrombolytic therapy in ischemic stroke measured by single-photon emission computed tomography. *Stroke* 1994;25:79–85.

18. Giubilei F, Lenzi GL, Di Piero V, et al. Predictive value of brain perfusion single-photon emission computed tomography in acute ischemic stroke. *Stroke* 1990;21:895–900.

19. Shimosegawa E, Hatazawa J, Inugami A, et al. Cerebral infarction within six hours of onset: prediction of completed infarction with technetium-99m-HMPAO SPECT. *J Nucl Med* 1994;35:1097–1103.

20. Raynaud C, Rancurel G, Tzourio N, et al. SPECT analysis of recent cerebral infarction. *Stroke* 1989;20:192–204.

21. Park SK, Grzybicki D, Lin HL, Murphy S. Modulation of inducible nitric oxide synthase expression in astroglial cells. *Neuropharmacology* 1994;33:1419–1423.

22. Endoh M, Maiese K, Wagner J. Expression of the inducible form of nitric oxide synthase by reactive astrocytes after transient global ischemia. *Brain Res* 1994;651: 92–100.

23. Skyhøj Olesen T, Larsen B, Herning M, Bech Skriver E, Lassen NA. Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence for an ischemic penumbra in patients with acute stroke. *Stroke* 1983;14:332–341.

24. Skyhøj Olesen T, Lassen NA. A dynamic concept of middle cerebral artery occlusion and cerebral infarction in the acute state based on interpreting severe hyperemia as a sign of embolic migration. *Stroke* 1984;15:458–468.

25. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol* 1991;29:231–240.

26. Marchal G, Serrati C, Rioux P, et al. PET imaging of cerebral perfusion and oxygen consumption in acute ischemic stroke: relation to outcome. *Lancet* 1993;341:925–927.

27. Jørgensen HS, Sperling B, Nakayama H, Raaschou HO, Skyhøj Olesen T. Spontaneous reperfusion of cerebral infarcts in patients with acute stroke. *Arch Neurol* 1994;51: 865–873.

28. Baird AE, Donnan GA, Austin MC, McKay WJ. Early reperfusion in the "spectacular shrinking deficit" demonstrated by single-photon emission computed tomography. *Neurology* 1995;45:1335–1339.

29. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. *J Neurosurg* 1991;74:407–414.

30. Stringer WA, Hasso AN, Thompson JR, Hinshaw DB, Jordan KG. Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: demonstration by xenon-enhanced CT. *AJNR* 1993;14:475–484.

31. Macfarlane R, Moskowitz MA, Sakas DE, Tasdemiroglu E, Wei EP, Kontos HA. The role of neuroeffector mechanisms in cerebral hyperperfusion syndromes. *J Neurosurg* 1991;75:845–855.

32. Heiss WD, Huber M, Fink GR, et al. Progressive derangement of periinfarct viable tissue in ischemic stroke. *J Cereb Blood Flow Metab* 1992;12:193–203.

33. Limburg M, van Royen EA, Hijdra A, Verbeeten B Jr. Regional cerebral blood flow SPECT in brain infarction: when does it predict outcome? *J Nucl Med* 1991;32:382–387.

34. Limburg M, van Royen EA, Hijdra A, de Bruïne JF, Verbeeten BWJ Jr. Single-photon emission computed tomography and early death in acute ischemic stroke. *Stroke* 1990;21:1150–1155.

35. Davis SM, Chua MG, Lichtenstein M, Rossiter SC, Binns D, Hopper JL. Cerebral hypoperfusion in stroke prognosis and brain recovery. *Stroke* 1993;24:1691–1696.

36. Hanson SK, Grotta JC, Rhoades H, et al. Value of single-photon emission-computed tomography in acute stroke therapeutic trials. *Stroke* 1993;24:1322–1329.

Temporal Lobe Perfusion Asymmetries in Schizophrenia

James M. Russell, Terrence S. Early, James C. Patterson, Justin L. Martin, Javier Villanueva-Meyer and Molly D. McGee

Departments of Psychiatry and Behavioral Science and Radiology, Division of Nuclear Medicine, The University of Texas Medical Branch, Galveston, Texas

Structural and functional neuroimaging techniques have consistently demonstrated that abnormal lateralization of temporal lobes may be important in identifying the pathophysiologic processes in schizophrenia. The exact nature of these reported abnormalities has not been consistent. **Methods:** We examined temporal lobe perfusion using HMPAO-SPECT in 22 individuals with schizophrenia in an effort to establish whether temporal lobe perfusion asymmetry is seen in these individuals, as compared to a group of 22 age- and sex-matched controls. **Results:** We found that the asymmetry index, a measure of perfusion differences between two homologous compared areas, was lower (more negative) in schizophrenic individuals. The asymmetry indices of patients considered with the results from globally corrected ROI means indicated that the left temporal lobes of individuals with schizophrenia were significantly hypoperfused when compared to controls. This finding does not appear to be caused by medication effects, demographic variables, handedness, imaging artifacts or analysis techniques. **Conclusion:** In our sample, patients with schizophrenia appear to have significant left hypoperfusion relative to right of their temporal lobes. Abnormal lateralization of temporal lobe blood flow may have important clinical implications by assisting with diagnosis and appropriate treatment for individuals with schizophrenia.

Key Words: schizophrenia; temporal lobe; SPECT; laterality; neurophysiology

Kraeplin et al. (*1*) originally hypothesized that abnormalities in the temporal lobe are pathophysiologically related to some schizophrenic symptoms. Flor-Henry et al. (*2*) demonstrated that temporal lobe epileptics with left-sided foci tended to have a schizophrenic-like psychosis, while those with right-sided foci were more likely to have manic-depressive symptoms. Later studies of psychosis following cerebral trauma, tumors and infections have continued to strengthen the association between schizophrenia and the left temporal lobe (*3*).

Reduced temporal lobe volume, with the left generally more frequent than right, and the presence of language abnormalities have implicated dysfunction of the temporal limbic cortex in individuals with schizophrenia (*3–8*). Functional neuroimaging studies, utilizing PET and SPECT, have consistently reported temporal lobe perfusion abnormalities in the brains of individuals with schizophrenia (*9–17*). The results of these studies are