

## Cerebral Perfusion Index

A New Marker for Clinical Outcome in Acute Stroke

**Andrei V. Alexandrov, MD**

Stroke Research Unit  
Sunnybrook Health Science  
Centre  
University of Toronto  
Toronto, Canada

**Lisa E. Ehrlich, MD**

Department of Nuclear  
Medicine  
Sunnybrook Health Science  
Centre

**Christopher F. Bladin, MD**

Stroke Research Unit  
Sunnybrook Health Science  
Centre

**John W. Norris, MD, FRCP**

Stroke Research Unit  
Sunnybrook Health Science  
Centre

### ABSTRACT

Single-photon emission computed tomography (SPECT) and transcranial Doppler (TCD) ultrasound are of good prognostic value in acute stroke, and combined they may be an accurate way to determine a target group of patients with maximum therapeutic response. Seventy consecutive patients were studied (42 with middle cerebral artery strokes, 18 with transient ischemic attacks [TIAs]; 10 were excluded due to failure of intonation). Two SPECT studies were performed at  $2.1 \pm 1.2$  and  $13.8 \pm 3.1$  days after onset. Serial TCD studies were done at 10 hours and at the time of the SPECT studies. Neurological deficit was scored on admission and 2 weeks later (using the Canadian Neurological Scale). Cerebral perfusion index (CPI) was derived by multiplying the values for TCD and SPECT patterns. Positive correlation was obtained in all 16 patients in whom cerebral angiography was performed within the first 3 days after onset. The occlusive TCD pattern and absence of perfusion on SPECT were common in the stroke group (19/42 patients) and were never seen in those with TIAs. A normal TCD pattern and normal perfusion on SPECT were more common in the patients with TIAs (9/18 vs 8/42,  $p = 0.02$ ; 5/10 vs 1/40,  $p = 0.0003$ ). The occlusive TCD and SPECT patterns were associated with the highest mean infarction volume ( $147 \pm 87$  vs  $19 \pm 21$ ,  $p < 0.0001$ ) and all nonocclusive TCD and SPECT patterns were associated with the better short-term outcome ( $43.2 \pm 33.9$  vs  $92.4 \pm 20.2$ ,  $p < 0.0001$ ). A tendency for hyperfixation of the tracer to be more common in

cardioembolic stroke was found. The three grades of the initial CPI (1–5, 6–12, 15–20) were found to predict different degrees of short-term outcome (good, medium, and poor). The TCD and SPECT combination (CPI) may prove to be a safe, fast, and reliable noninvasive substitute for angiography.

Alexandrov AV, Ehrlich LE, Bladin CF, Norris JW. Cerebral perfusion index: a new marker for clinical outcome in acute stroke. *J Neuroimag* 1993;3:209–215

At present, there is no definitive treatment for acute ischemic stroke; cytoprotective and thrombolytic therapies are the most promising [1]. Cerebral angiography and computed tomography (CT) are used in the immediate phase of stroke to determine patients suitable for intra-arterial or intravenous thrombolysis [2–4]. Arteriography is the “gold standard” but is invasive, time-consuming, and impractical in many cases. CT is not sensitive enough to show cerebral ischemia within the first hours [5, 6].

Single-photon emission computed tomography (SPECT) and transcranial Doppler (TCD) ultrasound allow noninvasive assessment of cerebral perfusion and are informative and of good predictive value in acute stroke [7–10]. Since acute thrombus formation and arterial occlusion are present in more than 70% of stroke patients within the first 6 hours [11], a combination of TCD and SPECT studies in the immediate phase may be an accurate and informative way of determining a target group of patients for maximum thrombolytic efficacy. Therefore, acute study to correlate serial TCD and SPECT measurements in acute and subacute phases of cerebral ischemia was carried out.

Received Nov 13, 1992, and in revised form Feb 2, May 7, and May 21, 1993. Accepted for publication May 22, 1993.

Address correspondence to Dr Alexandrov, Stroke Research Unit, 2075 Bayview Ave, Toronto, Canada M4N 3M5.

## Subjects and Methods

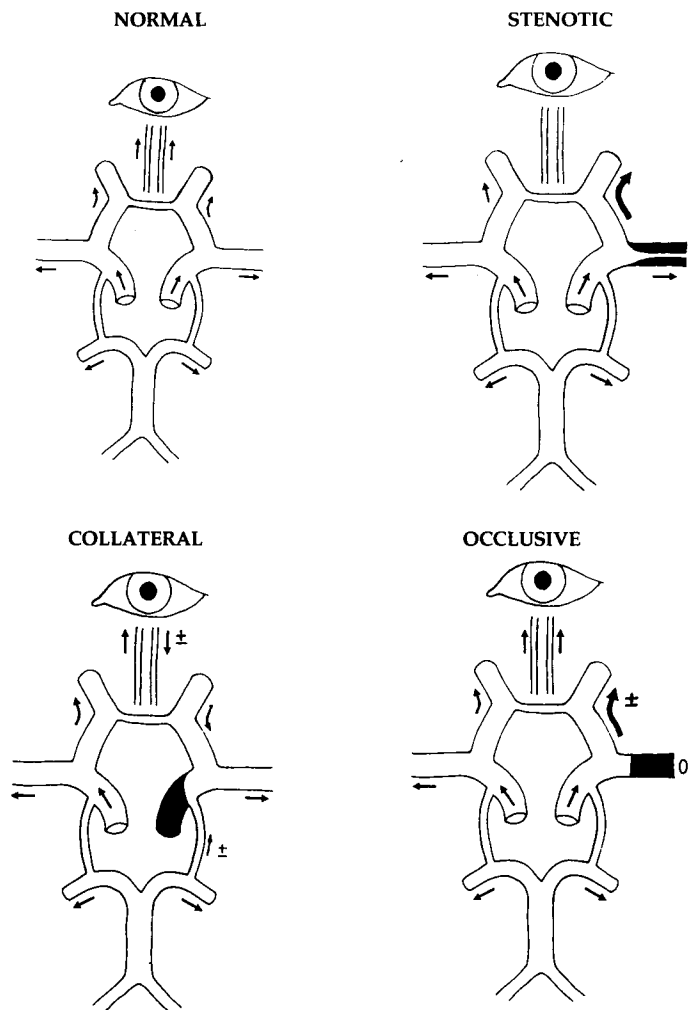
Consecutive patients with symptoms of middle cerebral artery (MCA) stroke admitted to the emergency department within 24 hours after onset were studied. CT was performed twice: on admission and at 3 to 4 days after onset. The volume of the ischemic lesion was measured by a special software program (Sigma Scan, Jandel Scientific, Corte Madera, CA). Two SPECT studies were performed in the subacute period (days 1–3 and 14) using technetium 99m-hexamethylpropyleneamineoxime (HMPAO, Amersham, UK). Serial TCD measurements were performed on admission and at the time of the SPECT studies (TC-2-64 EME). For SPECT, the following patterns of fixation of HMPAO were used: normal, high, mixed, low, and severe perfusion deficit (SPD) (i.e., absence of perfusion); for TCD, the following were used: normal, collateral, stenotic, and occlusive (Fig 1). An index representing cerebral perfusion was constructed by combining TCD and SPECT results. TCD reflects patency of arteries in the circle of Willis, and the authors' own comparison with angiographic controls and that of others [12, 13] indicate it is fairly accurate. SPECT reflects perfusion of brain parenchyma and previous reports indicate that this is also accurate [8, 10]. By combining the two techniques, the accuracy of diagnosis of perfusion deficits and the reason for their presence may be increased. The term "cerebral perfusion index" (CPI) is used (Table 1). Neurological deficit was scored by means of the Canadian Neurological Scale (CNS) [14] on admission and 2 weeks later. The risk of cardiogenic embolism was estimated using the Toronto Embolic Scale (TES) [15], which combines clinical and laboratory findings.

TCD reports were analyzed independently of other clinical and laboratory data, SPECT results were reported by a neuroradiologist (L. E. E.) who was unfamiliar with the clinical findings, and scoring of neurological deficit was performed by a neurologist (C. F. B.) who was unaware of the TCD and SPECT results.

Carotid duplex sonography was performed in all patients. No patient was treated with thrombolytic agents.

## Results

Seventy consecutive patients were studied: 10 were ex-



**Fig 1.** TCD patterns of flow direction and velocities of the circle of Willis in acute stroke.

cluded from the study because of technical failure of ultrasound insonation or because they were uncooperative; 42 had completed strokes (mean age,  $73.6 \pm 11.9$  yr; 25 men, 17 women) and 18 had hemispheric TIAs ( $73.8 \pm 12.1$  yr; 9 men, 9 women). In the stroke group, 5 patients died within the first 2 weeks. The mean time of the initial TCD was  $10.3 \pm 4.1$  hours (strokes) and  $10.1 \pm 6.2$  hours (TIAs) correspondingly. Mean time of the first SPECT and interim TCD studies was  $2.1 \pm 1.2$  days. The second SPECT and "final" TCD studies were done at  $13.8 \pm 3.1$  days after onset. In the TIA group, only the first TCD/

**Table 1.** Cerebral Perfusion Index (CPI): SPECT Pattern  $\times$  TCD Pattern

Patterns	TCD Values			
	4 (Normal)	3 (Collateral)	2 (Stenotic)	1 (Occlusive)
SPECT values				
5 (normal)	20	15	10	5
4 (high)	16	12	8	4
3 (mixed)	12	9	6	3
2 (low)	8	6	4	2
1 (absence of perfusion)	4	3	2	1

Table 2. TCD and SPECT Perfusion Patterns in Stroke and TIA Groups

Patterns	Initial (TIA)	Interim	Final
<b>TCD</b>			
Normal	8 (9)	11	15
Collateral	4 (3)	6	8
Stenotic	11 (6)	17	13
Occlusive	19 (0)	6	2
Total	42 (18)	40	38
<b>SPECT</b>			
Normal	—	1 (5)	0
High	—	9 (3)	11
Low	—	11 (2)	18
Absence of perfusion	—	19 (0)	2
Total	—	40 (10)	31

SPECT study was available: The neurological deficit resolved in the majority of TIA patients at the time of the initial TCD study and they were not admitted to the hospital. Table 2 summarizes the TCD and SPECT findings in both groups.

**Correlation with Cerebral Angiography:** Cerebral angiography was performed in 16 patients within the first 3 days after onset. Two MCA occlusions, 2 MCA stenoses, 2 developed collaterals, and 1 normal result were found in 7 stroke patients. Three MCA stenoses, 2 developed collaterals, and 4 normal results were found in 9 patients with TIAs. In all patients, cerebral angiography was reviewed independently by a radiologist and the reports confirmed the TCD and SPECT findings. The numbers are too small to apply statistical methods to estimate the sensitivity and specificity.

**Presumed Middle Cerebral Artery Occlusion and Severe Perfusion Deficits:** The occlusive TCD pattern was common in the stroke group (19/42 patients) and was not seen in the TIA group (0/18 patients). A normal TCD pattern was prevalent in the TIA group (9/18 vs 8/42,  $p = 0.02$ ).

Increasing numbers of stenotic, collateral, and normal patterns reflected spontaneous resolution of MCA occlusion on TCD ( $n = 19$ ). The majority of initial occlusions ( $n = 13$ ) transformed into stenoses within the subacute phase. Sixty-eight percent of initial MCA occlusions re-

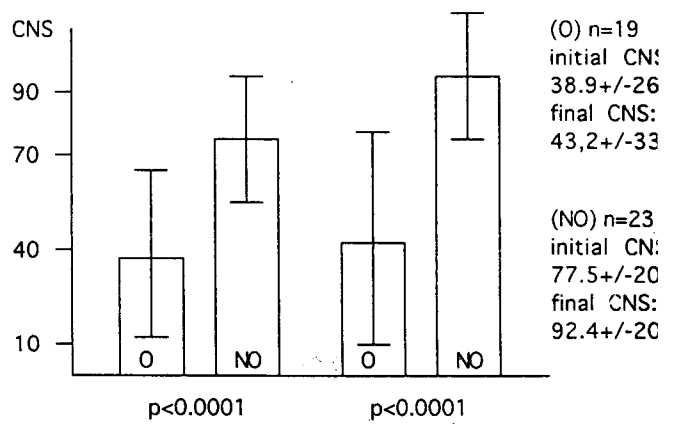


Fig 2. Canadian Neurological Scale (CNS) scores in occlusive (O) and nonocclusion (NO) groups at first 10 hours and at 2 weeks after onset.

solved in 2 days and 91%, in 2 weeks. Sixty-four percent of initial MCA stenoses resolved in 2 weeks.

Absence of perfusion on SPECT (SPD) was detected in 19 of 40 stroke patients and was not seen in the TIA group (0/10 patients). Normal perfusion pattern on SPECT was more common in the TIA group (5/10 vs 1/40,  $p = 0.0003$ ).

**The Association Between TCD and SPECT Patterns:** TCD and SPECT results (Table 3) were compared. A strong correlation was obtained in cases of initial TCD occlusions and SPDs but there was no correlation between results of interim and final TCD studies to the first or second SPECT studies.

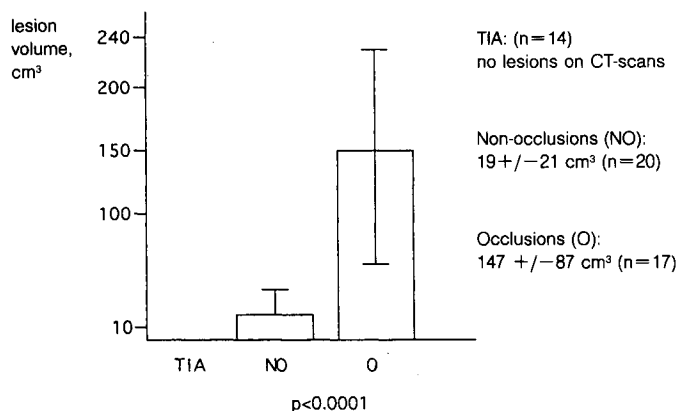
**The Association Between TCD and SPECT Patterns and Neurological Deficit Scoring:** Neurological deficit scores (on the CNS) on admission and 2 weeks later were compared between 19 patients with SPD/TCD occlusions and those with other strokes ( $n = 23$ ) (Fig 2). All nonocclusive TCD and SPECT patterns were associated with the better short-term outcome; there was no significant difference between them.

**Comparison of CT, SPECT, and TCD:** The volume of the ischemic lesion was measured on later CT scans (> 7 days). All available CT scans in the TIA group ( $n = 14$ ) were negative. Stroke patients were divided into two

Table 3. TCD and SPECT Patterns of Perfusion in the Stroke Group

	Initial TCD/First SPECT				Interim TCD/First SPECT				Final TCD/Second SPECT			
	N	H	L	SPD	N	H	L	SPD	N	H	L	SPD
N	—	2	5	—	—	3	5	2	—	5	7	—
C	—	2	2	—	—	3	2	1	—	3	3	—
S	1	5	4	—	1	3	4	10	—	3	8	—
O	—	—	—	19	—	—	—	6	—	—	—	2

TCD: N = normal; C = collateral; S = stenotic; O = occlusive. SPECT: N = normal; H = high (including mixed); L = low; SPD = severe perfusion deficit (absence of perfusion).



**Fig 3.** Mean volume of ischemic lesion in transient ischemic attack (TIA) and stroke subgroups.

groups: those with occlusions (n = 17) and those with other patterns (n = 20). Mean infarction volumes were compared between these groups (Fig 3). In 15 patients the first SPECT study was done after negative findings on the admission CT and prior to the second positive CT study (see Case Reports). In 12, SPECT showed perfusion defects corresponding to the lesions (in 3 patients hyperperfusion was found and it was difficult to compare images).

**Hyperperfusion in Cardioembolic Stroke:** Forty-two strokes were subdivided etiologically into four groups according to the following criteria:

1. Cardioembolic—22 patients—high TES score, e.g., atrial fibrillation
2. Atherothrombotic—5 patients—more than 70% stenosis of ipsilateral internal carotid artery (ICA) (carotid duplex)
3. Lacunar—3 patients—clinical and CT criteria
4. “Cryptogenic”—12 patients—no obvious cause was found

In the TIA group, 6 TIAs were cardioembolic; 5, atherothrombotic; and 7, of unrevealed cause.

The distribution of SPECT types of perfusion versus etiology was analyzed, and there was a tendency for hyperperfusion of HMPAO to be more common in cardioembolic versus other types of stroke and TIAs—14 high and

**Table 5.** Cerebral Perfusion Index (CPI) Predicts Short-Term Outcome (2 Weeks)

CPI*	CNS at 2 Weeks	n	p
15–20	111.5 ± 7.4	10	0.01 0.001
6–12	85.3 ± 32.5	19	
1–5	50.2 ± 34.7	22	

\*CPI: 15–20 = good; 6–12 = medium; 1–5 = poor. CNS = Canadian Neurological Scale.

mixed versus 23 low and normal patterns, compared to 8 versus 36 in the nonembolic group (n = 81)—but it was not significant.

**CPI as a Predictor of Short-Term Outcome:** Recovery of the neurological deficit was subdivided into the following groups:

1. Complete (with CNS score at 2 weeks—115)
2. Good (≥90–115)
3. Partial (≥50–90)
4. Poor (<50)

The mean values of CNS scores on admission and the index derived from the first SPECT and initial TCD in each group of patients above were compared (Table 4). There was no correlation between CNS scores at 2 weeks and CPIs derived from other TCD and SPECT results. Furthermore, the three grades of CPI (1–5, 6–12, 15–20) were compared to the short-term outcomes (mean CNS scores at 2 weeks after onset), and a strong association between them and different degrees of the recovery was found (Table 5).

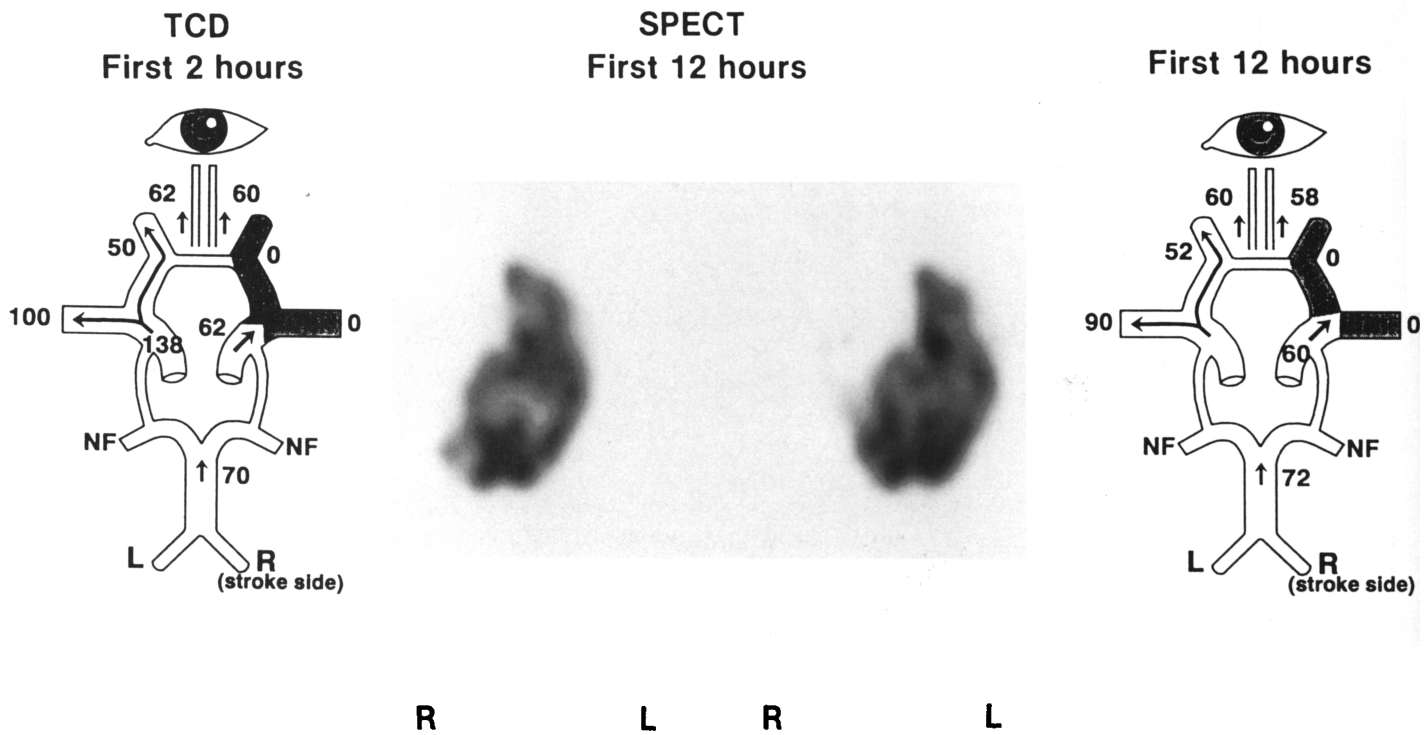
### Case Reports

**Patient 1:** An 82-year-old woman with a history of cardiac disease was admitted within the first 2 hours after sudden onset of left-sided hemiplegia. The CNS score on admission was 45. The TES indicated a high risk of cardioembolism (atrial fibrillation). An occlusive TCD pattern (asonic right MCA and anterior cerebral artery [ACA], and a flow in right ICA syphon) was detected. CT demonstrated negative findings at 3 hours after onset. SPECT was performed 12 hours after onset and showed

**Table 4.** Predicting Value of Neurological Deficit Scoring on Admission and Cerebral Perfusion Index (CPI) Derived from the First SPECT and Initial TCD

Recovery at 2 Weeks (CNS)	Predictors					
	Initial CNS	n	p	CPI	n	p
Complete (115)	75.4 ± 22.7	22	NS 0.002 <0.0001	13.2 ± 5.7	12	0.01 0.005 0.007
Good (≥90–115)	84.2 ± 12.2	13		8.3 ± 3.8	13	
Partial (≥50–90)	68.2 ± 11.5	12		4.1 ± 3.0	12	
Poor (<50)	22.1 ± 8.9	13		1.4 ± 1.4	13	

CNS = Canadian Neurological Scale; NS = not significant.



**Fig 4.** Occlusive TCD pattern and severe perfusion deficit on SPECT at 2 to 12 hours after onset of hemiplegia (see Case Report 1). NF = not found.

an absence of perfusion in the entire right MCA and ACA territories. The initial CPI was 1. TCD showed persistence of MCA and ACA occlusions till the patient died the next day (Fig 4). Cerebral infarction in the right MCA and ACA territories was confirmed at autopsy.

**Patient 2:** A 73-year-old woman with a history of previous hemispheric TIAs was admitted within 14 hours after onset of right-sided hemiparesis and global aphasia. The CNS score on admission was 35. The TES indicated a low risk of cardioembolism. The initial and interim TCD studies showed an occlusive pattern. CT demonstrated negative findings at 16 hours after onset. SPECT was performed at 24 hours and showed an absence of perfusion in the left MCA and ACA territories. The initial CPI was 1. Repeat CT scan was done on the fourth day and revealed infarction in the corresponding territory (infarction volume, 112.9 cm<sup>3</sup>). The second SPECT study was performed on the 14th day and prominent hyperfixation of the tracer was noted. The final TCD study showed a patent left MCA and ACA (normal pattern) (Fig 5). The CNS score at 2 weeks remained 35 and the patient had a poor recovery, presumably due to late and ineffective recanalization.

#### Discussion

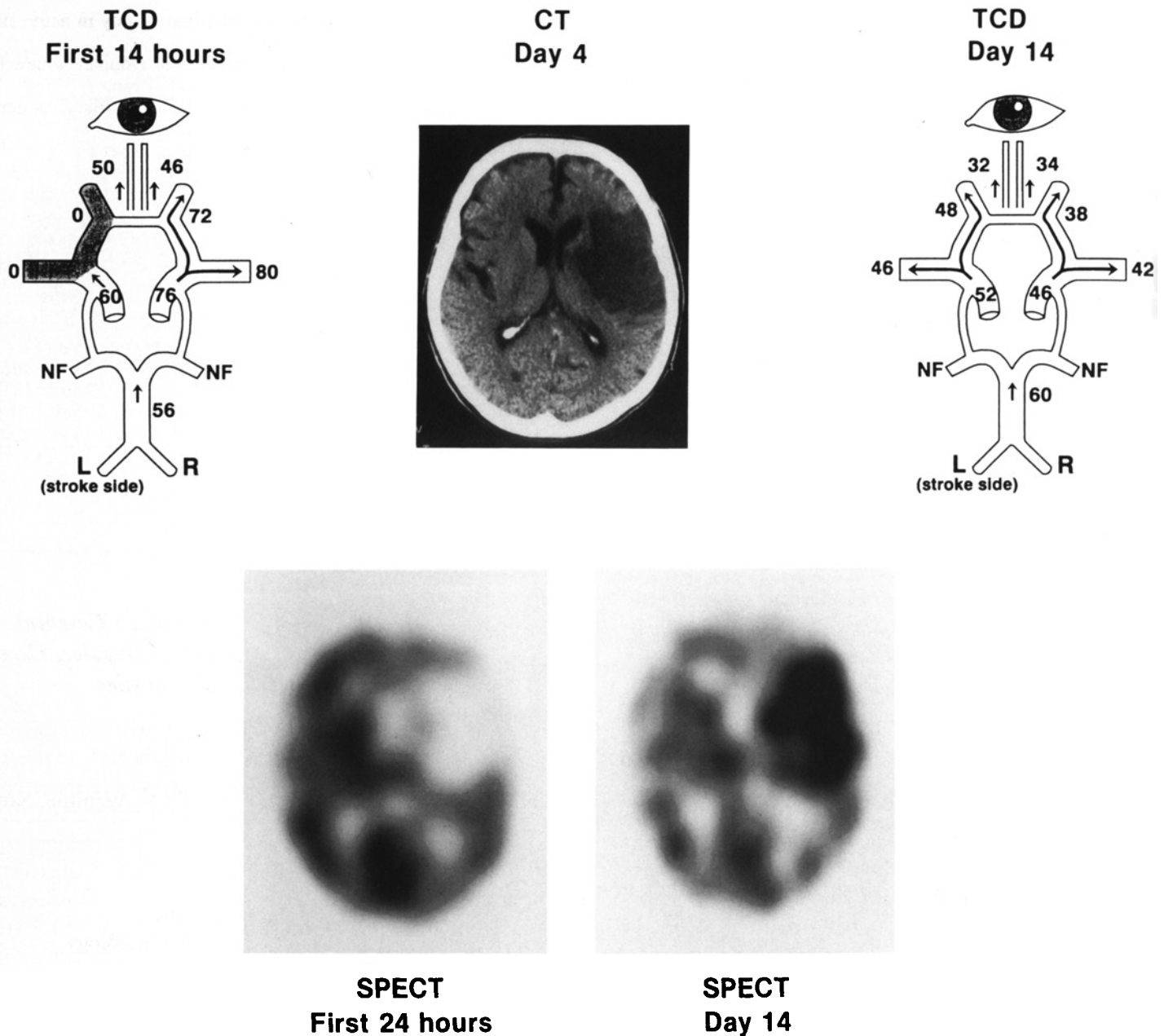
This study showed that TCD and SPECT patterns in stroke and TIA are quite different. Strokes are associated with up to 50% TCD/SPECT occlusive patterns at 10

hours after onset, which correlates with angiographic findings [11]. These patterns were never seen in the TIA group where normal perfusion patterns are more common. Presumably it reflects the underlying pathogenesis.

In this study, only the initial TCD correlated with SPECT findings (occlusive TCD pattern = absence of perfusion on SPECT) while there was no significant correlation between interim and final TCD and SPECT studies in spite of them being done at the same time. Only 6 presumed occlusions persisted on TCD up to the time of the first SPECT, when absence of perfusion was detected in 19 patients. So far, other TCD patterns displayed all possible SPECT patterns and vice versa. This may be the reason why late or single TCD results are difficult to correlate with subacute SPECT.

Luxury perfusion sometimes occurs in acute stroke [16–18]. The present study showed that hyperfixation of HMPAO on SPECT could be detected in up to 25% of both stroke and TIA patients, which is slightly higher than previously reported [17]. There is also a tendency for the high and mixed HMPAO fixation SPECT patterns to be more common in cardioembolic stroke. These results correlate with the authors' previous findings in two subacute SPECT studies involving 191 consecutive stroke patients: High, particularly mixed patterns were prevalent at day 3 and 2 weeks after onset in cardioembolic strokes [19].

Serial TCD and SPECT studies seem to relate to outcome. Occlusive patterns were found in all types of is-



**Fig 5.** TCD and SPECT patterns within 2 weeks of onset of hemiparesis and global aphasia associated with poor recovery. CT demonstrates left middle cerebral artery infarction (see Case Report 2). NF = not found.

chemic stroke except lacunar and were associated with the poorest short-term outcome. High and low SPECT patterns as well as normal, collateral, or stenotic TCD patterns were associated with better short-term outcome compared to the recovery of patients in the occlusive group. Presumably this represents early recanalization.

CPI values of 1 through 5 are presumably associated with arterial occlusions and medium values (6–12), with various combinations of reduced perfusion due to stenosed arteries or poor collaterals, possibly with low metabolism. High values of CPI (15–20) were associated with normal or sufficient collateral perfusion and possibly with normal or high metabolism. The predictive value of CPI derived from the initial TCD and first SPECT

study was better than the initial clinical scoring (on the CNS), and CPI provides information on a mechanism of ischemia as well. Its predictive value in the immediate phase of cerebral ischemia (within the first 6 hours) needs to be evaluated prospectively. This index may prove clinically useful to identify the target group of patients with maximum therapeutic response to thrombolysis in trials designed without cerebral angiography.

In conclusion, TCD and SPECT have several promising advantages. Previous works have shown that TCD is a reliable method in the diagnosis of MCA trunk lesions in acute stroke compared to angiography [12, 13], while SPECT is more sensitive than CT in the acute phase of stroke [5, 6]. Good predictive value was dem-

onstrated for both methods if performed acutely [8–10, 14]. The present study supports these findings, and serial TCD and SPECT could contribute to the management of thrombolytic therapy. Their combination (CPI) may prove to be a safe, fast, and reliable noninvasive substitute for angiography.

---

This work is supported by Sunnybrook Trust for Medical Research Foundation. Dr Alexandrov is a Postgraduate Research Fellow from the Institute of Neurology, Academy of Medical Sciences, Moscow, Russia.

The authors are grateful to Sandra E. Black, MD, FRCP(C), Beverly Bowyer, RN, and Philippa Johnston, BA, for their invaluable help and assistance.

---

## References

1. Norris JW. Drug treatment of acute cerebral infarction. In: Krigelstein J, ed. Proceedings of the Second International Symposium on Pharmacology of Cerebral Ischemia. Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1989:439
2. Hennerici M, Hacke W, von Kummer R, et al. Intravenous tissue plasminogen activator for the treatment of acute thromboembolic ischemia. *Cerebrovasc Dis* 1991;1(suppl 1):124–128
3. Brott TG, Clarke Haley E Jr, Levy D, et al. Urgent therapy for stroke: Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992; 23:632–641
4. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78–86
5. Yeh SH, Liu RS, Hu HH, et al. Brain SPECT imaging with <sup>99</sup>Tc-hexamethylpropyleneamine oxime in the early detection of cerebral infarction: comparison with transmission computed tomography. *Nucl Med Commun* 1986;7:873
6. Feldmann M, Voth E, Henze Th, et al. Significance of HMPAO-SPECT in the early diagnosis and followup of acute cerebral ischemia—comparison to CCT. *Psychiatry Res* 1989;29:457–458
7. Mountz JM, Modell JG, Foster ML, et al. Prognostication of recovery following stroke using the comparison of CT and technetium-99m HM-PAO SPECT. *J Nucl Med* 1990;31:61–66
8. Limburg M, van Royen EA, Hijdra A, Verbeeten B Jr. r-CBF-SPECT in brain infarction: when does it predict outcome? *J Nucl Med* 1991;32:382–387
9. Kushner MJ, Zanette EM, Bastianello S, et al. Transcranial Doppler in acute hemispheric brain infarction. *Neurology* 1991;41:109–113
10. 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
11. Fieschi C, Argentino C, Lenzi GL, et al. Clinical and instrumental evaluation of patients with ischemic stroke within the six hours. *J Neurol Sci* 1989;91:311–322
12. Zanette EM, Fieschi C, Bozzao L, et al. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke* 1989;20:899–903
13. Kaps M, Damian MS, Teschendorf U, Dorndorf W. Transcranial Doppler ultrasound findings in middle cerebral artery occlusion. *Stroke* 1990;21:532–537
14. Cote R, Hachinski VC, Shurvell BL, et al. The Canadian

- Neurological Scale: a preliminary study in acute stroke. *Stroke* 1986;17:731–737
15. Norris JW, Zhu CZ. Transcranial Doppler: a new test for cerebral embolism? In: Yao JST, Pearce WH, eds. Technologies in vascular surgery. Philadelphia: Saunders, 1992:166–173
  16. De Roo M, Mortelmans L, Devos P, et al. Clinical experience with Tc-99m HMPAO high resolution SPECT of the brain in patients with cerebrovascular accidents. *Eu J Nucl Med* 1989;15:9–15
  17. Moretti JL, Gilles D, Cinotti L, et al. “Luxury perfusion” with 99m-Tc-HMPAO and 123-I-Imp SPECT imaging during the subacute phase of stroke. *Eur J Nucl Med* 1990;16:17–22
  18. Leonard J-P, Nowotnik DP, Neirinckx R. Technetium-99m-d,1-HM-PAO: a new radiopharmaceutical for imaging regional brain perfusion using SPECT—a comparison with iodine-123 HIPDM. *J Nucl Med* 1986;27:1819–18
  19. Alexandrov AV, Pirisi A, Black SE, et al. Value of single photon emission computed tomography in acute stroke. *Ann Neurol* 1992;32:237 (Abstract)
- 

## *8th International Symposium on Cerebral Hemodynamics: Transcranial Doppler, Cerebral Blood Flow, and Other Modalities*

*Date:* February 14–17, 1994

*Place:* Hyatt Regency La Jolla at Aventine, San Diego, CA

*Contact:* Arlene Wiedel  
Conference Coordinator  
Institute of Applied Physiology  
and Medicine  
701 16th Avenue  
Seattle, WA 98122  
Tel: (206) 553-7330; Fax: (206) 553-1717