Confirmation of CT criteria to distinguish pathophysiologic subtypes of cerebral infarction.

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Confirmation of CT Criteria to Distinguish Pathophysiologic Subtypes of Cerebral Infarction

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PURPOSE: To determine whether cerebral infarctions classified as embolic or hemodynamic by their appearance on CT scans reflect distinct pathophysiologic entities. **METHODS:** Cerebral infarctions were retrospectively classified into two groups according to their morphologic appearance on CT scans: territorial infarctions and watershed, or terminal supply area, infarctions. Specific CO_2 reactivity for both groups of patients was determined with the xenon-133 method and 32 stationary detectors. Twenty-one patients with unilateral, supratentorial, ischemic cerebral infarctions were selected. CT findings were highly suggestive of a territorial infarction in 14 patients (mean age, 56 years) and of a watershed infarction in seven patients (mean age, 52 years). **RESULTS:** The initial slope index of the territorial and watershed infarction groups during CO_2 inhalation was 55.1 ± 2.4 sec^{-1} and 52.0 ± 1.9 sec^{-1}, respectively, in the infarcted hemispheres and 58.3 ± 2.3 sec^{-1} and 55.1 ± 1.5 sec^{-1}, respectively, in the noninfarcted hemispheres. CO_2 reactivity of the unaffected detectors was 1.75 ± 0.3 sec^{-1} mm Hg^{-1} and 1.51 ± 0.2 sec^{-1} mm Hg^{-1} for the territorial and watershed infarction groups, respectively. CO_2 reactivity of the affected detectors was 1.75 ± 0.3 sec^{-1} mm Hg^{-1} and 1.27 ± 0.2 sec^{-1} mm Hg^{-1} for the two groups, respectively. The CO_2 reactivity difference between affected detectors of the hemodynamic group and age-matched healthy control subjects was significant. **CONCLUSIONS:** The difference in CO_2 reactivity between the two groups supports the concept that CT criteria can identify two pathophysiologic entities. In addition, we conclude that during the chronic stage, lower CO_2 reactivity of the watershed infarction indicates that the global hemodynamic situation in these infarcts is more severely compromised than in territorial infarctions.

Index terms: Brain, computed tomography; Brain, infarction

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Cerebral infarctions of embolic origin are caused by a sudden occlusion of an artery resulting from an embolus from the heart, the major cerebral arteries, or the aortic arch (1). The infarcted tissue is located in the center of a vascular territory; for example, in the region of the basal ganglia supplied by the stem of the middle cerebral artery or its major branches or in the region of cortical gray matter supplied by pial arteries (2, 3).

Unilateral, hemodynamically induced infarcts (watershed) are primarily caused by occlusion or severe stenosis of a carotid artery with a systemic hypotensive episode (4–12). Their exact pathogenesis has been disputed (11). The clinical presentation possibly gives some indication of the hemodynamic pathogenesis of an infarction. Sometimes episodic, fluctuating or progressive weakness and shaking of a lower limb in the absence of amaurosis fugax have been reported to be indicative of hemodynamic events (5–8). Syncope at the onset of symptoms, often precipitated by postural changes, in the presence of a contralateral carotid occlusion, has also been reported to be associated with cerebral infarctions of hemodynamic origin

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(13–16). Most investigators, however, agree that clinical features are unreliable for making precise distinctions between the two groups. Ringelstein et al (3) and others (2, 17–19) specified criteria using cranial computed tomography (CT) to identify these two types of infarcts. However, single case studies have suggested that some infarcts located in watershed areas might be caused by emboli (11, 20); thus, these CT criteria have not been readily accepted by all investigators (20).

The CO_2-challenge test has been widely used in the area of cerebrovascular research and patient treatment (21, 22). Differences between testing CO_2 reactivity and autoregulation have recently been described (23–25). Vasoreactivity tests are widely used to determine the hemodynamic reserve in patients with carotid occlusive disease (8, 23, 25–29), transient ischemic attacks (14, 26), or other types of stroke (30).

Our intention in this study was to determine whether cerebral infarctions classified as embolic or hemodynamic by their appearance on CT scans truly reflect distinct pathophysiologic entities. Territorial infarctions and watershed infarctions were categorized according to CT criteria (3, 17–19). Our hypothesis was that CT criteria truly reflect two distinct pathophysiologic entities should CO_2 reactivity be different in both groups.

Materials and Methods

Subjects

Subjects were identified retrospectively from laboratory records of regional cerebral blood flow (rCBF) measurements. Between 1986 and 1993, CO_2-challenge tests were performed in stroke patients who were either hospitalized or seen on an outpatient basis. rCBF measurements with CO_2 were not performed within the first 2 weeks after onset of acute symptoms to avoid potentially harmful side effects of CO_2 inhalation (31). At the time of the present evaluation, a CT study was available in 54 stroke patients who underwent a CO_2 test. Patient eligibility was contingent on the presence of unilateral, supratentorial, ischemic cerebral infarction and a CT study compatible with either territorial or watershed/terminal supply area infarction. On the basis of the CT criteria described below, seven male patients (mean age, 52 years; range, 46 to 65 years) were identified in whom CT scans showed a lesion that was compatible with a watershed infarction, and 14 patients were identified who had CT findings compatible with territorial infarction (12 men, two women; mean age, 56 years; range, 41 to 71 years). Table 1 displays the findings in the carotid arteries obtained with the use of Doppler sonography and angiography. Selective angiography was performed in five patients in the territorial infarction group and in four patients in the watershed infarction group.

TABLE 1: Grading of carotid disease in 14 patients with territorial infarctions and seven with watershed or terminal supply area infarctions

	Territorial Infarctions		Watershed or Terminal Supply Area Infarctions	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Occlusion	7 ICA	1 MCA	1 ICA	. . .
Filiform	1 ICA	1 ICA	2 ICA	1 ICA
>70% stenosis	1 ICA	1 ICA	2 ICA	. . .
<70% stenosis	. . .	2 ICA	. . .	. . .
Plaques	1 ICA	1 ICA	. . .	. . .
No abnormalities	4	8	2	6

Note.—ICA indicates internal carotid artery; MCA, middle cerebral artery.

CT Evaluation

Without prior knowledge of the rCBF results, a neuroradiologist categorized the cerebral infarctions into two groups: one consisted of territorial infarction and the other of watershed/terminal supply area infarction. Categorization by CT criteria paralleled those described by Ringelstein et al and others (3, 17–19). Cerebral infarctions were classified as watershed infarction when they were located between the long penetrating cortical and striatocapsular branches (deep watershed infarction), in the supply area terminating in periventricular white matter (terminal zone infarction), or in border zones between the anterior and middle cerebral artery or between the posterior and middle cerebral artery (anterior or posterior border zone infarction, respectively). Cerebral infarctions were called territorial infarction when they were restricted to territories supplied by major intracerebral arteries, their branches, or pial arteries (territorial infarction). The description set forth by Damasio (32) was used to identify vascular territories.

In the territorial infarction group, hypodensities were situated in the territory of the left (five) and right (four) middle cerebral artery, and in the right (four) and left (one) posterior cerebral artery (Fig 1). In the watershed infarction group, four were in the anterior border zone (two on each side) and three were in the terminal zone (two were right sided, one was left sided) (Fig 2).

rCBF Measurements

rCBF measurements were obtained by use of the intravenous xenon-133 technique (33–35). After intravenous application of 25 mCi xenon-133, clearance curves were recorded for 11 minutes by 32 stationary NaJ detectors located bilaterally over homologous brain regions (Cerebrograph 32c, Novo Diagnostic Systems, Copenhagen, Denmark). Upon completion of the steady-state measure-

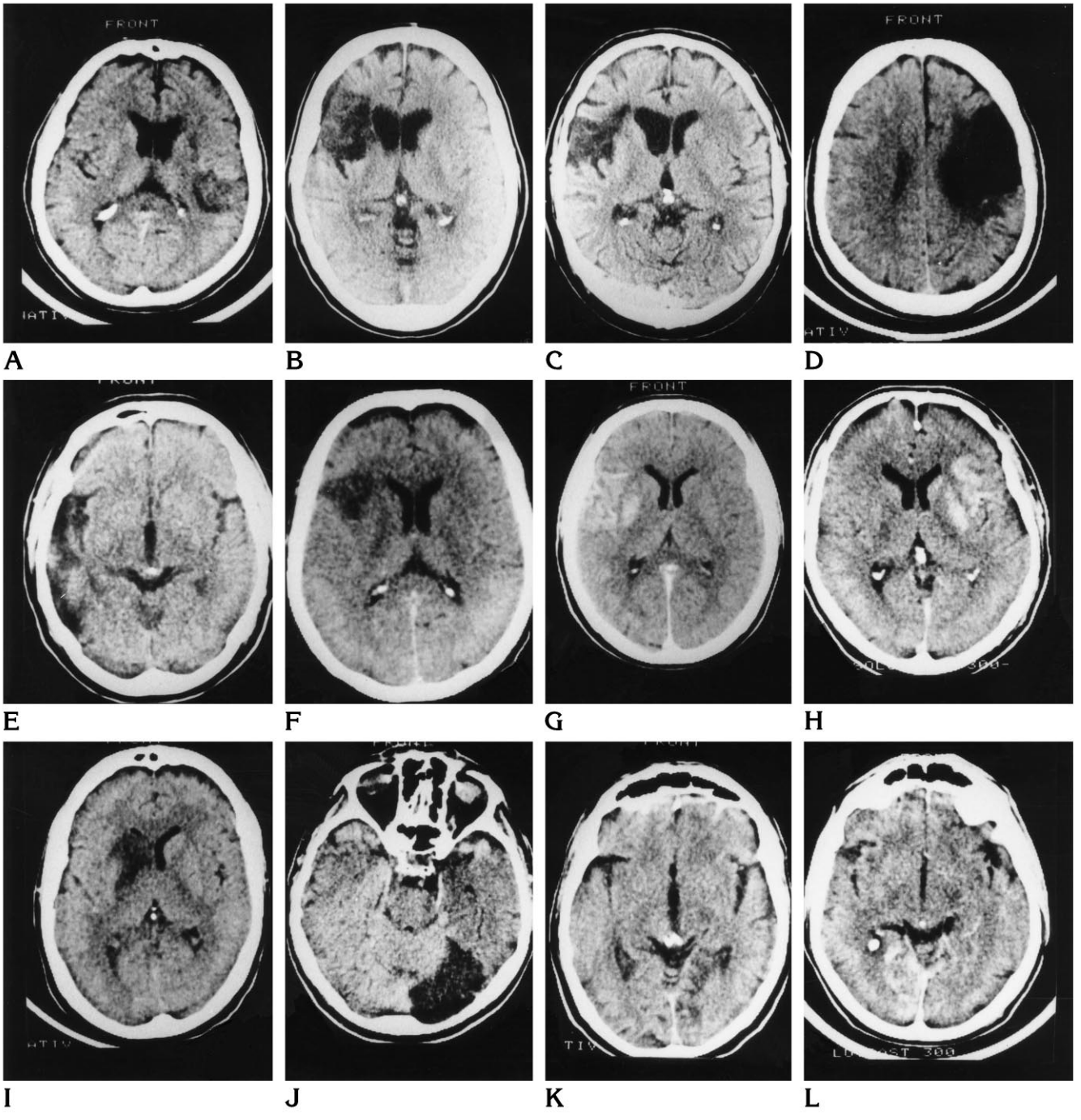

Fig 1. Representative CT scans of 12 patients with territorial strokes, selected to depict the largest extent of the stroke in each patient, show territorial infarctions of the middle cerebral artery (*A–H*), nucleus lentiformis infarction (*I*), and territorial infarctions of the posterior cerebral artery (*J–L*). *G, H*, and *L* show acute disruption of the blood-brain barrier after contrast enhancement.

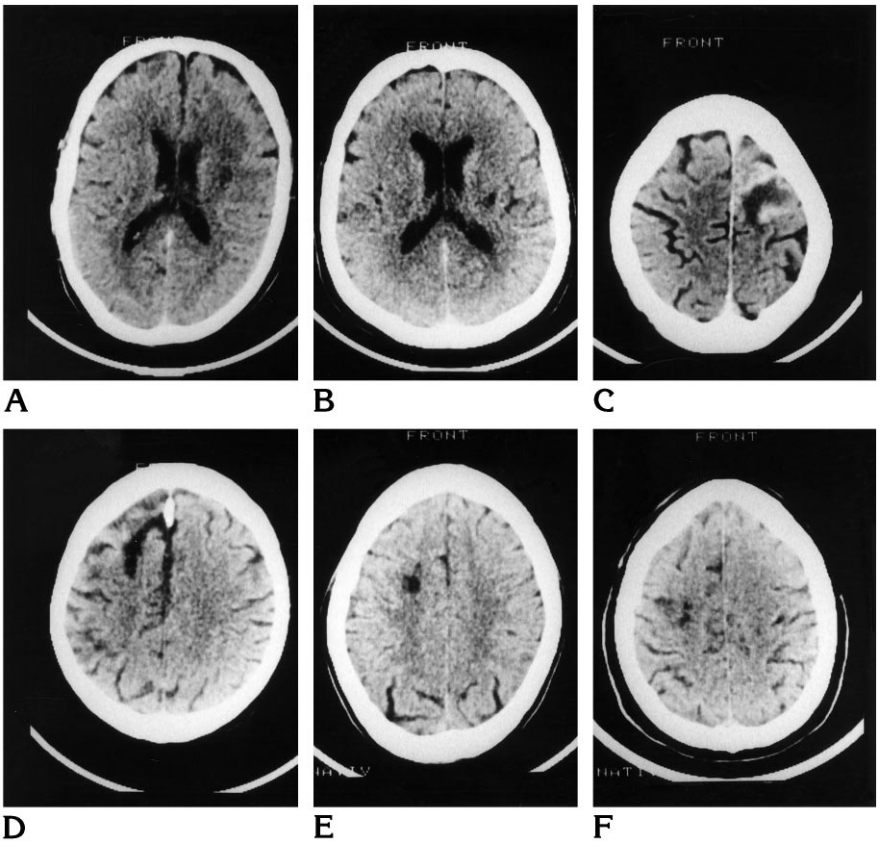

Fig 2. Representative CT scans of six patients with watershed infarction show terminal supply area infarctions (*B* and *F*) and anterior border zone infarctions (*A, C, D, E*). *C* shows blood-brain barrier disturbances after contrast enhancement. Because only one plane is displayed, it is not obvious that terminal supply area infarcts (*B*) might be restricted to two or three planes whereas striatocapsular infarcts tend to penetrate deeply into the hemisphere and have a more wedge-shaped appearance.

ment at normocapnia and that of remaining background activity, a second measurement was obtained during inhalation of 5% CO_2 in room air. CO_2 inhalation started 1 minute before the application of xenon-133 and continued for 5 minutes. End-expiratory CO_2 concentration was continuously recorded and converted to $Paco_2$. rCBF analysis was limited to the initial slope index (ISI) computed from the early decay of clearance curves between 0.5 and 1.5 minutes. The ISI reflects gray and white matter flow, but is predominated by gray matter flow (36–38). Vasoreactivity was expressed as specific CO_2 reactivity as defined by Davis et al (39): CO_2 reactivity was calculated as a ratio of change in rCBF to change in $Paco_2$ ISI(2) − ISI(1)/ $Paco_2(2) - Paco_2(1)$ sec^{-1} mm Hg^{-1}.

Control measurements were calculated as global and hemispheric values from 21 age-matched subjects (mean age, 55 years; range, 40 to 68 years) culled from 60 healthy volunteers without vascular risk factors (S. Kreil, *Messung der Normalwerte von Hirndurchblutung und CO_2-Reaktivität mit der intravenösen 133 Xenontechnik*, Bonn, Germany: Rheinische Friedrich-Wilhelms-Universität; 1992, dissertation).

Statistics

Group results are presented as mean values ± standard error of the mean (SEM). Means of groups were compared by unpaired *t* tests (SPSS, Chicago, Ill).

Results

The global ISI was 50.6 ± 2.8 sec^{-1} during normocapnia in the healthy age-matched control subjects and 71.4 ± 3.8 during CO_2 inhalation. CO_2 reactivity was 2.11 ± 0.1 sec^{-1} mm Hg^{-1}.

rCBF values in the affected and unaffected hemispheres of both groups of patients were lower than control values during normocapnia and hypercapnia ($P < .01$, Table 2). The ISI during normocapnia in the territorial infarction group was not significantly different from that of the watershed infarction group (40.6 ± 2.2 versus 39.3 ± 2.5 in the affected side, 42.7 ± 1.5 versus 40.8 ± 2.1 in the noninfarcted hemispheres). During inhalation of 5% CO_2, The ISI was 55.1 ± 2.4 and 52.0 ± 1.9 in the infarcted hemispheres of the territorial infarction and watershed infarction groups, respectively. The ISI in the noninfarcted hemispheres was 58.3 ± 2.2 and 55.1 ± 1.5 in the two groups, respectively. CO_2 reactivity of the territorial infarction and watershed infarction groups was 1.75 ± 0.3 and 1.31 ± 0.2 in the infarcted hemispheres and 1.92 ± 0.3 and 1.45 ± 0.2 in the noninfarcted

TABLE 2: Initial slope index (ISI, sec^{-1}) for the infarcted and noninfarcted hemispheres of the territorial and watershed/terminal supply zone infarctions during normocapnia and hypercapnia compared with global values of age-matched control subjects

	Normocapnia				Hypercapnia			
	Infarcted		Noninfarcted		Infarcted		Noninfarcted	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
ISI								
Terminal	40.6	2.5	42.7	1.5	55.1	2.4	58.3	2.2
Watershed	39.3	2.5	40.8	2.1	52.0	1.9	55.1	1.5
Control	. . .	. . .	50.6	2.8	. . .	. . .	71.4	3.8
$Paco_2$								
Terminal	35.5	1.2	. . .	. . .	45.0	1.2	. . .	. . .
Watershed	35.6	1.6	. . .	. . .	46.4	1.6	. . .	. . .
Control	37.8	1.4	. . .	. . .	47.6	1.6	. . .	. . .

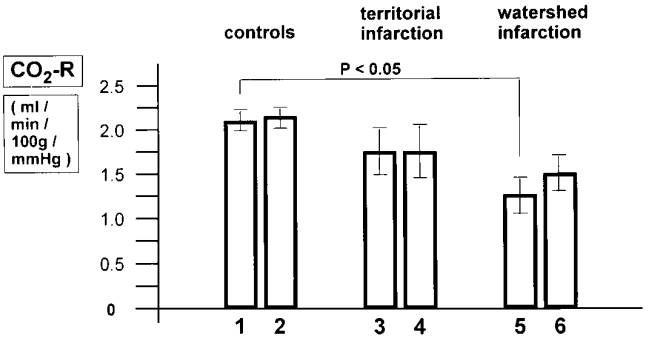

Fig 3. Regional CO_2 reactivity (*CO_2-R)* in healthy subjects (columns 1 and 2) and in the affected (columns 3 and 5) and unaffected (columns 4 and 6) regions of the infarcted hemispheres (columns 3 to 6). Columns 3 and 4 represent territorial infarcts, columns 5 and 6 watershed/terminal supply area infarcts. CO_2 reactivity is calculated as a ratio of change in rCBF to change in $Paco_2$. Columns represent mean values ± SEM. Notice the significant decrease of CO_2 reactivity of the affected detectors in the infarcted hemispheres of the watershed group compared with healthy age-matched control subjects (columns 1 and 2).

hemispheres, respectively (nonsignificant difference). In each patient, four or five regional detectors directed toward the location of the infarct on the CT scans were categorized as being affected and those outside the infarcted tissue as unaffected. CO_2 reactivity of the unaffected regions was 1.75 ± 0.3 (158 detectors) and 1.51 ± 0.2 (77 detectors) for the territorial infarction and watershed infarction groups, respectively. CO_2 reactivity of the affected regions was 1.75 ± 0.3 (66 detectors) and 1.27 ± 0.2 (35 detectors) in the two groups, respectively. The CO_2 reactivity difference between patients with watershed infarction and healthy volunteers was significant ($P < .05$, Fig 3). There was a trend for the affected detectors to have a lower CO_2 reactivity in the watershed group than in the territorial group ($P < .09$).

In terms of interpreting the data, note that the volume of all territorial (cerebral) infarctions was strikingly larger than that of the watershed infarctions (Figs 1 and 2).

Discussion

The xenon-133 method is based on recordings of clearance curves of a radioactive tracer from brain tissue. Since the full-width half-maximum of xenon-133 is only 13 to 18 mm (D. Lange, A. Hartmann, P. Schenck, "Der Einfluß der Gamma-Streuung im Gewebe auf 133 Xe-rCBF-Messungen mit der Anger-Kamera," presented at the annual meeting of the Society of Nuclear Medicine, Copenhagen, Denmark, 1977) and the detectors are stationary, rCBF values mainly represent tissue perfusion of superficial structures. Tissue, which is normally perfused, is more strongly weighted for calculation of rCBF values than is slowly perfused or ischemic tissue (look-through phenomenon) (40). Cross-talk from the noninfarcted hemisphere enhances the effect, and interhemispheric differences are underestimated (8). The present investigation was not intended to evaluate the pathophysiologic basis of stroke in individual patients by means of cerebral angiography, echocardiography, or postmortem pathology. Furthermore, the scatter of normal values of the xenon-133 method and the overlap of pathologic and normal CO_2 reactivity drastically limit the diagnostic value in specific patients. This is even more so because the xenon-133 method, as compared with local blood flow measurements, does not truly reflect contrasting CO_2 reactivity in infarcted and unaffected tissue in patients with an acute arterial occlusion (31).

A concentration of 5% CO_2 was selected to

ensure that the $Paco_2$ increase was large enough to induce a significant rCBF increase but not unpleasant during inhalation. An inhalation time of 5 minutes was used to allow ISI to be calculated from a part of the clearance curve, which was recorded during inhalation of CO_2.

Some particular types of cerebral infarct are difficult to detect by CT using morphologic criteria. Dorsally or peripherally located striatocapsular infarcts may be indistinguishable from deep terminal zone infarcts (41, 42). Posterior border zone infarcts have a less elongated shape than anterior border zone infarcts and may be confused with embolic infarctions in the posterior aspect of the middle cerebral artery territory (17). Variability of vascular territory may also contribute to pitfalls in identifying different, pathophysiologic types of infarcts with CT (43).

Our control values of CO_2 reactivity (2.1 sec^{-1} mm Hg^{-1}) were calculated from an age-adjusted group of healthy volunteers (S. Kreil, *Messung der Normalwerte. . .)* and fell within the same range as described by Young et al (38). CO_2 reactivity of the infarcted (1.75 sec^{-1} mm Hg^{-1}) and unaffected (1.91 sec^{-1} mm Hg^{-1}) hemispheres of the territorial infarction was not significantly lower than in the healthy volunteers. Both watershed infarction hemispheres had decreased CO_2 reactivity (1.60 and 1.31 sec^{-1} mm Hg^{-1}). The separate evaluation of unaffected and affected detectors demonstrated that CO_2 reactivity surprisingly appeared to be quite homogeneous within each infarcted hemisphere of the territorial infarction group. The affected regions within the infarcted hemispheres of the watershed infarction group, however, had slightly lower CO_2 reactivity than the unaffected regions ($P = .056$). The watershed infarctions, which manifested as small CT lesions as compared with those of the territorial infarction cohort, had a decreased regional CO_2 reactivity above the lesions, which was absent in the territorial infarctions. The major finding relates to CO_2 reactivity of the affected detectors, which was significantly lower than in age-matched control subjects, but not in the embolic group. What might have caused the difference in CO_2 reactivity?

The volume of infarction differed in both groups. We believe that it is not reasonable to assume that the size of the cerebral infarctions might have caused the difference in CO_2 reactivity. It is extremely unlikely that lower CO_2 reactivity caused smaller infarcts than higher CO_2 reactivity. It is also unlikely that smaller infarcts caused a more pronounced reduction of CO_2 reactivity than larger ones. Thus, it is unlikely that the different infarct volumes in the two groups caused different CO_2 reactivity. By definition, the location of the infarcts was different in each group. While 13 of 14 infarcts in the territorial infarction group involved the cortex, this was the case in only three of seven infarcts in the watershed infarction group. From a methodologic point of view, the larger and more superficially located territorial infarction should affect the xenon-133 clearance curves more than the smaller and more deeply located watershed infarction. Thus, it is rather unlikely that localization caused a diminished CO_2 reactivity of the watershed infarction group. The degree of extracranial, internal carotid artery stenosis cannot explain decreased CO_2 reactivity in hemodynamic infarcts, since there was a higher number of carotid occlusions in the embolic group (Table 1). Another confounding factor is a nonsignificant age difference between the groups. Once again, it is unlikely that the younger age of the watershed infarction cohort caused a decrease of CO_2 reactivity. To our understanding, the most reasonable explanation for the difference in CO_2 reactivity between the stroke groups is that different pathophysiologic mechanisms underlie the events. We assume that the watershed infarctions with diminished CO_2 reactivity are low-flow infarcts or infarcts of hemodynamic origin, as originally proposed (18, 19). The territorial infarctions probably have an embolic origin.

Weiller et al (42) compared CO_2 reactivity as determined by single-photon emission CT in embolic and hemodynamic infarcts. Their study was based on calculations of interhemispheric ratios without absolute flow data. They reported that a reduced flow in the infarcted tissue of hemodynamic infarcts was less severe during the acute stage than it was in embolic strokes. This corresponds to the disappearance of CO_2 reactivity in the affected territory seen after acute occlusion of the middle cerebral artery in primates (31). Furthermore, Weiller et al (42) reported that in the remaining noninfarcted tissue, CO_2 reactivity was more severely impaired in hemodynamic than in embolic strokes, paralleling the results of our study. They suggested that comparatively small lesions of hemody-

namic infarcts visible on CT scans simply represent the "tip of an iceberg."

Two studies using transcranial Doppler sonography investigated CO_2 reactivity in different types of strokes. Maeda et al (44) compared CO_2 reactivity in stroke patients with severe carotid stenosis or occlusion with CO_2 reactivity in patients who had no carotid stenosis and presented with cortical, presumably embolic, cerebral infarctions. CO_2 reactivity was lower in the group with severe carotid disease. The authors concluded that CO_2 reactivity tests might help to characterize different types of ischemic lesions. However, it was not clear to us whether strokes in these patients with severe carotid obstruction were of hemodynamic or embolic origin. Their differences of CO_2 reactivity may be explained by the presence or absence of carotid occlusion and not necessarily by the type of stroke. Kleiser et al (45) studied 106 stroke patients with carotid occlusion. They divided their patients into three groups according to the origin of infarction—lacunar, embolic, and hemodynamic—and suggested that an exhausted CO_2 reactivity favors a hemodynamic origin of infarction.

Several investigators have evaluated the hemodynamics in watershed infarcts by using positron emission tomography (PET). Yamauchi et al (46) described an increase of the oxygen extraction fraction and a decrease of the CBF/cerebral blood volume ratio in the watershed areas in patients with unilateral internal carotid artery occlusion. They extended their observations to a group of patients with transient ischemic attacks or minor stroke with high-intensity lesions in the deep white matter as determined with MR imaging (47). They found similar changes of blood flow and oxygen extraction fraction as in their previous study and concluded that the lesions were indicative of hemodynamic compromise. Leblanc et al (9) reported similar findings predominantly in the anterior border zone in seven patients with unilateral carotid artery occlusion and transient ischemic attack or minor stroke. Carpenter et al (48) could not support these findings in a group of patients who had carotid occlusion and normal CT findings and who were not further selected for potentially hemodynamic events. Levine et al (14) divided patients who had had a clinically determined transient ischemic attack into a subset of hemodynamic and nonhemodynamic cerebral infarctions. They described a lower CO_2 reactivity on the affected side in the group with hemodynamic rather than nonhemodynamic infarctions. Earlier studies comparing PET with xenon perfusion studies (15, 49, 50) suggested that an increased oxygen extraction fraction and a decreased CBF/cerebral blood volume ratio correspond to regions with diminished CO_2 reactivity.

In conclusion, our results support the concept that CT criteria are useful for distinguishing between two pathophysiologic infarct types. Hemodynamic reserve capacity of global flow is more severely impaired in hemodynamic infarctions than in embolic infarctions.

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