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Failure to Identify Cerebral Infarct Mechanisms from Topography of Vascular Territory Lesions

Michael Hennerici, Michael Daffertshofer, and Lothar Jakobs

PURPOSE: Our purpose was to determine whether topographic patterns of ischemic damage seen on brain imaging studies are useful for evaluating different mechanisms of infarction and for distinguishing embolic from hemodynamic disorders.

METHODS: Early CT scans were reviewed to identify brain infarctions in the middle cerebral artery territory in 800 patients with either significant obstructive lesions of the internal carotid artery (70% stenosis, n = 17; occlusion, n = 85) or nonvalvular atrial fibrillation (n = 186) as the only identified source of stroke. Ninety-nine CT studies were considered suitable for entry into the final analysis. The scans were digitized and superimposed on postmortem brain sections by matching algorithms to display the variability of the cerebrovascular territories.

RESULTS: Cortical borderzone-type infarctions were rare and evenly distributed among patients with cardiac sources of embolism (3.2%) and severe carotid obstructions (3.6%). In contrast, subcortical borderzone infarcts occurred significantly more often in patients with carotid obstructive disease (36% versus 16%). However, on computerized segmentation analysis, the topography of infarction was the same in both groups.

CONCLUSION: The current concept that stroke mechanisms can be inferred from interpretation of stroke patterns on brain scans is heavily confounded by the variability in intracranial arterial territory distributions. Since individual arterial territories cannot be identified *in vivo*, interpretation of stroke topography is invalidated. In particular, the cortical wedge-type of borderzone infarction, said to result from hemodynamic compromise in low-flow perfusion territories, is an ambiguous observation and may be seen in patients with cerebral embolism and hemodynamic compromise due to severe carotid disease.

Treatment of acute stroke has become a major area of clinical interest and research since preliminary studies have shown that fibrinolytic (1, 2) and neuroprotective (3) agents reduce the functional deficit of patients who present early after onset of symptoms. As the interval from the onset of stroke to the start of treatment increases, so does the likelihood of adverse events, at least if thrombolytic treatment is considered. Furthermore, risks and benefits of treatment are unevenly distributed among different stroke subtypes: the risk of secondary hemorrhage and parenchymal bleeding is highest in patients with hemodynamically significant obstructions in proximal large arteries, such as the internal carotid artery (ICA), and declines with distal location (4). Thus, patients with small territorial infarctions due mostly to embolism in distal arterial branches of the major cerebral arteries,

or even small-vessel disease, seem to derive the greatest benefit from early reperfusion treatment (1, 2, 4).

Because the window of opportunity for effecting early and complete clot resolution before tissue edema develops is narrow, knowledge about the particular vascular mechanisms involved is mandatory to avoid treatment in patients with proximal thrombosis and extensive low-flow tissue perfusion due to poor collateral circulation (4). One of the first determinations to be made, then, is the cause of stroke. According to a large, recently reported study, however (5), only two thirds of the initial clinical impressions of stroke subtypes agreed with the final determination, and this rate was similar for all subtypes (ie, large-artery disease with or without hemodynamic compromise often could not be separated from artery-to-artery and cardiac embolism or small-vessel disease). Since the means to identify sources of embolism or hemodynamic compromise (eg, vascular sonography, transesophageal echocardiography, MR imaging/MR angiography, helical CT) have not been available until recently, and because they are time-consuming and/or require some cooperation from the patients, these techniques have not been applied to the investigative

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repertoire of hyperacute stroke (1–3). Because infarct patterns seen on brain images have been considered a substitute for direct identification of the infarct mechanisms (6, 7), and because current stroke management will be facilitated by increasingly available MR perfusion and diffusion techniques (8, 9), attempts to apply and improve vascular tests to the examination of patients in the hyperacute phase of stroke might be pointless.

The present study challenges the concept that topographic stroke patterns as revealed by brain imaging studies represent markers for the identification of particular stroke mechanisms. This concept dates back to the 1950s, when Schneider and Zülch (10, 11) elegantly hypothesized the characteristic features of extraterritorial infarctions (ie, borderzone and boundary-zone compromise due to hemodynamic failure) versus territorial infarctions (ie, due to embolic mechanisms). CT analysis largely confirmed these postmortem studies (12), which suggested that cortical “watershed” infarction was due to carotid occlusion or severe stenosis in patients who had sustained a period of hypotension before the stroke (13, 14). Recent skepticism has cast a shadow on this concept, as the demonstration of anatomic variation in vascular territories has implied a remarkable inconsistency of extraterritorial areas in size and topography. Van der Zwan et al (15, 16) published maps of vascular variability based on autopsy series, in which they showed the large variability of the MCA, anterior cerebral artery (ACA), and posterior cerebral artery (PCA) territories. This raised the possibility that interpretations of individual infarct patterns might often be inaccurate when made solely on the basis of brain mapping studies (17–19).

Methods

We retrospectively reviewed the records of 880 patients who were included in the Nimodipine European Stroke Trial (NEST). A detailed description of the methods used in this study has already been described (20). In brief, in this European multicenter trial, patients in whom a clinical diagnosis of ischemic stroke in the territory of the MCA was made were randomized for administration of 120 mg of the calcium antagonist nimodipine versus a placebo. All patients had evidence of arrhythmia, particularly nonvalvular atrial fibrillation, as a cardiac source of embolism. Extracranial Doppler sonography was performed in all patients for the detection and classification of the degree of extracranial artery disease. Entry CT scans were obtained from 876 patients; however, 124 scans had to be excluded for findings inconsistent with the diagnosis of MCA infarction (often the only CT scan available was performed early and hence no lesion was visible). According to the Doppler sonograms of the extracranial arteries and the ECGs/echocardiograms of the patients whose records were reviewed for the present study, 102 had 70% obstructive lesions of the ICA (70% stenosis, $n = 17$; occlusions, $n = 85$) and at least 186 had nonvalvular atrial fibrillation as the only evident source of stroke. The average age was 68 years in the 150 men and 138 women prerecruited into the study.

According to the criteria used by the CT review panel in the NEST investigation, scans from patients with identified subtypes of stroke were selected only if clear signs of ischemic infarction in the MCA territory could be established from the first scan.

TABLE 1: Overview of patients in the study

	No.	Age, y	Sex Ratio, Male:Female
Cardiac source of embolism	63	72 \pm 7*	23:40
Significant carotid obstruction	36	64 \pm 11*	23:13
Both	99	69 \pm 10	46:53

* $P < .001$.

To enable a sufficient analysis for the present investigation, CT scans had to have section orientations parallel ($\pm 3^\circ$) to the intersection between the anterior and posterior commissures, according to the standard stereotactic approach of Talairach et al (21); a calibration scale as well as a gray scale had to be documented; and studies with major rotation of the patient's head were excluded. This protocol reduced the number of useful studies to 99 patients (Table 1).

All CT scans were digitized to make them congruent with corresponding van der Zwan brain sections (15, 16) (Fig 1). Images were analyzed off-line on a computer workstation. Because normalization was necessary, the digitized CT scans had to be two-dimensional, parallel to the corresponding postmortem brain sections, a procedure that was accomplished in two steps. First, two CT sections closely matching the van der Zwan sections at the caudate level and 12 mm below it were chosen. The cortical surface, basal ganglia, and ventricular structures of those individual CT scans were then segmented to serve as reference structures. Second, using an initial elliptical matching procedure for the cortical surface and a second planar elastic matching algorithm for the basal ganglia and ventricular structures, we matched the individual CT sections to the corresponding postmortem sections (22, 23).

Each infarcted area attributable to carotid disease and consistent with the patient's clinical signs and symptoms was identified, outlined, and superimposed automatically onto the corresponding cut in the standard brain section (Fig 2). All areas of infarction displayed on the two standard brain sections were then superimposed in a sandwichlike fashion, creating a composite image of all infarcted areas for each level respectively. A graphic composition was programmed to darken the regions in which infarcted areas overlapped. This resulted in a summation image comparable to the histogram, in which the areas with the greatest amount of overlap appeared the darkest on a white to black spectrum.

Superimposition of this summation image onto the minimal and maximal extension maps of the MCA, ACA, and PCA territories shown by van der Zwan et al (15, 16) was then performed for all infarcted areas at the levels of the thalamus, basal ganglia, and ventricular system, and summation images of infarcted areas were classified as territorial or extraterritorial (borderzone) patterns of infarction. Superficial territorial infarcts, deep territorial infarcts, superficial borderzone infarcts, and deep borderzone infarcts were distinguished. A superficial territorial infarct was characterized by a hypodense lesion compatible with ischemia in the territories of the three major cerebral arteries supplied by the main stem, the cortical or medullary branches; striatocapsular infarcts were also included in this group for their similar pathogenesis. A deep territorial infarct was defined as a hypodense lesion (diameter >15 mm). Borderzone infarcts were described as originally proposed (6, 7): a superficial borderzone infarction wedged between the ACA and MCA or MCA and PCA, and a deep borderzone area between the deep penetrating arteries and the medullary branches of corresponding major cerebral arteries. The analysis was performed separately for the minimal and the maximal territorial extensions according to the criteria described by van der Zwan et al (15, 16) at each of the two levels.

A χ^2 -test was used to compare discrete data. In cases of a small amount of sample data, the Fisher exact test was applied.

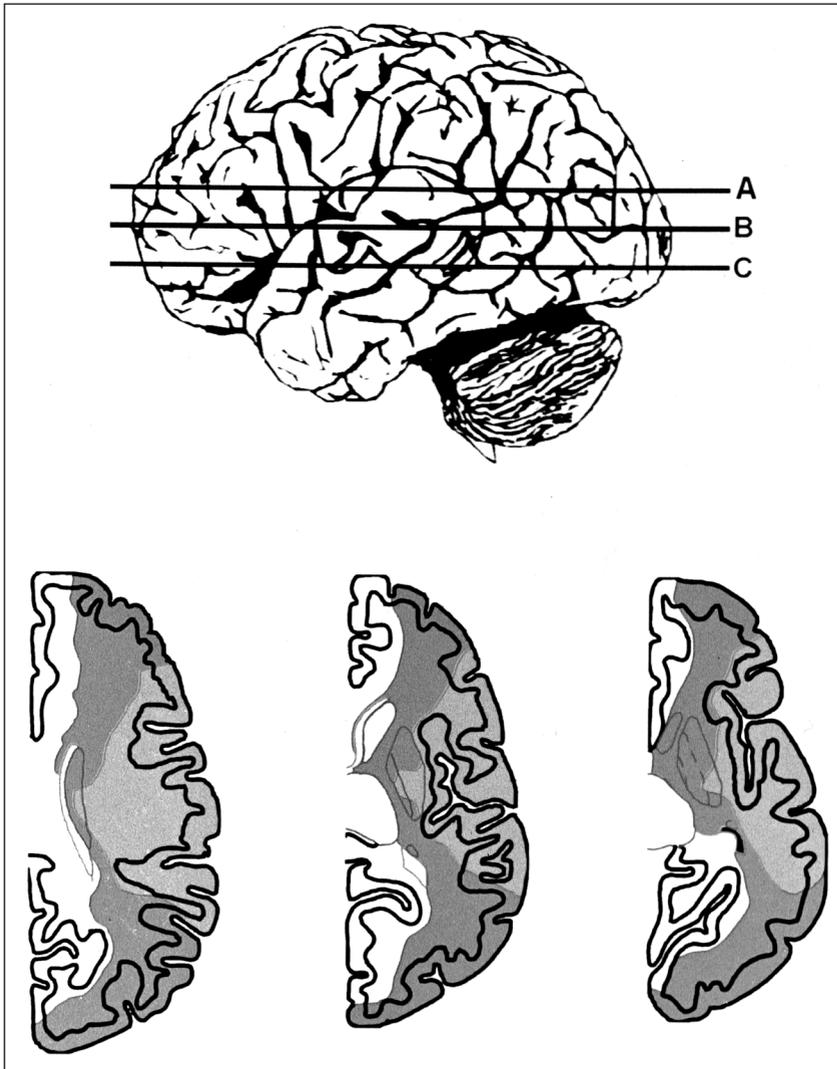


FIG 1. Diagram of section levels (top) corresponding to horizontal sections (bottom) showing the variable margins of the MCA territory. A, ventricular level; B, basal ganglia level; C, thalamic level. (Modified from [16].)

Results

Because patients were recruited from a stroke trial in which hemiparesis and a visible hemispheric infarction were inclusion criteria, all patients in each group had infarction patterns covering the nearest MCA territory. The minimum MCA territory was not exceeded in 15 patients (24%) who had a cardiac source of embolism and in six patients (17%) who had a hemodynamically relevant carotid obstruction as the underlying stroke mechanism. Thirty-six (57%) of the patients with a cardiac source of embolism and 16 (44%) of the patients with a carotid source of embolism had infarction patterns extending outside the variable area between the maximal and minimal MCA territory (Table 2). An analysis of the widest MCA territory (cortical/subcortical) showed that 12 patients with cardiac and significantly more patients with carotid ($n = 14$) ($P < .05$) infarct mechanisms (either cortical or subcortical infarction) had patterns exceeding this map.

Infarction classification and distribution are presented in Table 3. Extraterritorial cortical borderzone infarctions definitely tending beyond the widest MCA

territory were rare: two (3%) of the 63 patients with potential cardiac sources and one (4%, not significant) (in a patient who had an occlusion of the ICA) of the 36 patients with carotid obstructions. Patients with infarcts from severe carotid stenosis (6/8; 75%) and from carotid occlusion (24/28; 86%) similarly had patterns that exceeded the minimal MCA extension map and that possibly covered perfusion areas of the ACA or PCA. No differences could be identified in topography of the vascular territories affected. In contrast, subcortical borderzone infarcts occurred significantly more frequently in patients with carotid disease (13/36; 36%) than in patients with potential sources of cardiac embolism (10/63; 16%) ($P < .05$).

Consequently, overall territorial infarcts were significantly more frequent in patients with sources of cardiac embolism ($n = 51/63$; 81%) than in patients with significant carotid disease (21/36; 58%) ($P < .05$). However, according to the computerized segmentation analysis of the infarction topography, no difference in the topographic distribution between the two groups of potentially different pathomechanisms could be observed on the summation images

FIG 2. Illustration of the digitization procedure from CT scans. CT sections had to be congruent with the corresponding van der Zwan brain sections (15,16). First, the area of infarction was semiautomatedly identified (A and B). After fitting the individual cortical surface, basal ganglia, and ventricular structures to the digitized system (C), we superimposed the area of infarction onto the reference map (D).

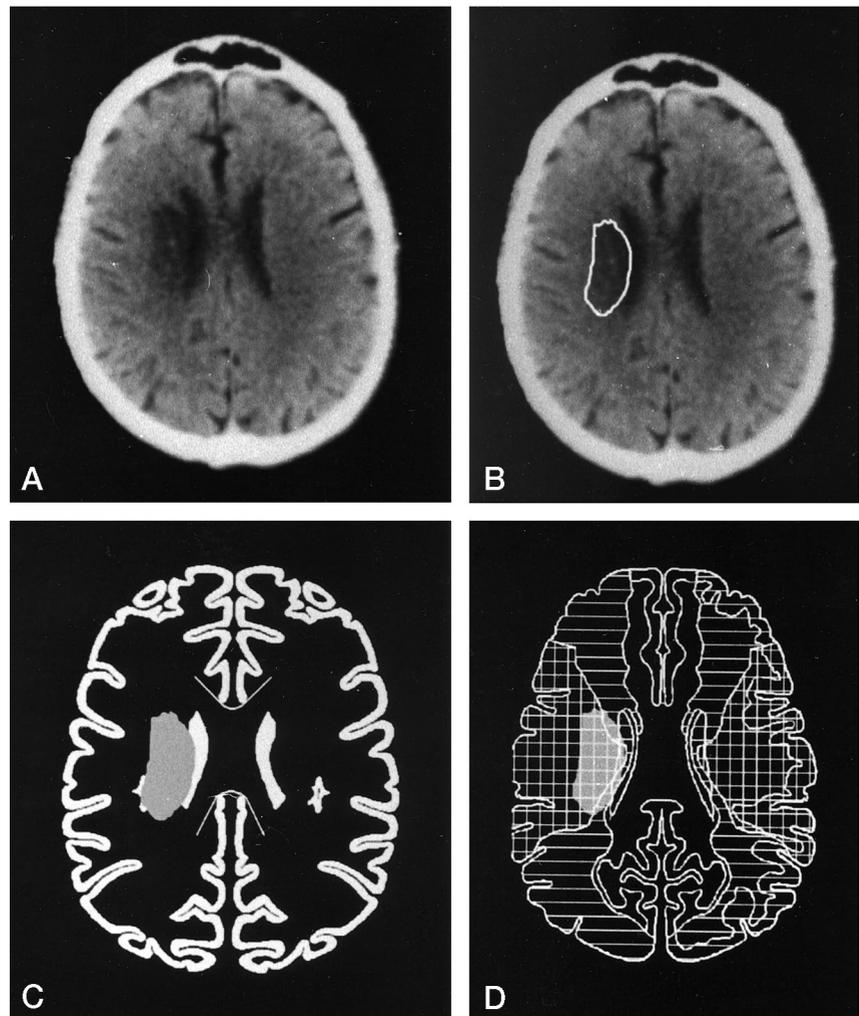


TABLE 2: Location of infarct pattern according to minimum/maximum MCA territories

	No. (%) of Infarcts Located Exclusively within Nearest MCA Territory	No. (%) of Infarcts Extending into the Variable MCA Territory	No. (%) of Infarcts Extending Outside the Widest MCA Territory	Total
Cardiac	15 (24)	36 (57)	12 (19)*	63
Carotid	6 (17)	16 (44)	14 (39)*	36

* $P < .05$.

(Figs 3 and 4, Table 2). Moreover, among patients with only subcortical extraterritorial infarctions, no difference in patterns of infarction could be observed between the two pathogenic mechanisms.

If the individual matching plots of the three patients with extraterritorial cortical infarcts were interpreted, all cases could be perceived as multiple territorial MCA infarcts, provided a large MCA territory according to the criteria provided by van der Zwan et al (15, 16) were assumed (Fig 5). Thus, using variable vascular territories, no single instance was found in either group of a definitely pure extraterritorial cortical borderzone infarction.

Discussion

Although not specific, watershed infarction, according to the original concept put forward by Schneider and Zülch (10, 11), was considered to represent a common pathomechanism of hemodynamic failure distal to severe large-vessel obstructive lesions. Further anatomic studies defined cortical and subcortical borderzone territories (13, 24), and several authors reported that watershed infarction occurs in about 19% to 64% of patients with severe carotid stenosis and occlusion (25–29). Sustained periods of hypotension in the presence of severe stenosis or, more often, occlusion of the carotid artery were regarded as the source of stroke. Observation of the superficially and/or deeply located borderzone infarctions was associated with carotid disease. The mechanism hypothesized was, however, only occasionally evidenced in these patients. Indeed, Howard et al (30) and Ross Russell and Bharucha (31) observed superficial “watershed infarctions” in patients without carotid disease after cardiopulmonary surgery but supposed that these were caused by hemodynamic insufficiency. Direct recordings from hundreds of microembolic events during open-heart surgery by means of transcranial Doppler sonography in recent years do not

TABLE 3: Classification of standardized cerebral infarction topography

	No. (%) of Extraterritorial Infarctions		No. (%) of Infarctions in the MCA Territory			
	Cortical	Subcortical	Cortical			Subcortical
			Middle	Anterior	Posterior	
Cardiac (n = 63)	2 (3)	10 (16)*	38 (75)	2	4	7 (14)
Carotid (n = 36)	1 (4)	13 (36)*	11 (52)	4	4	2 (10)

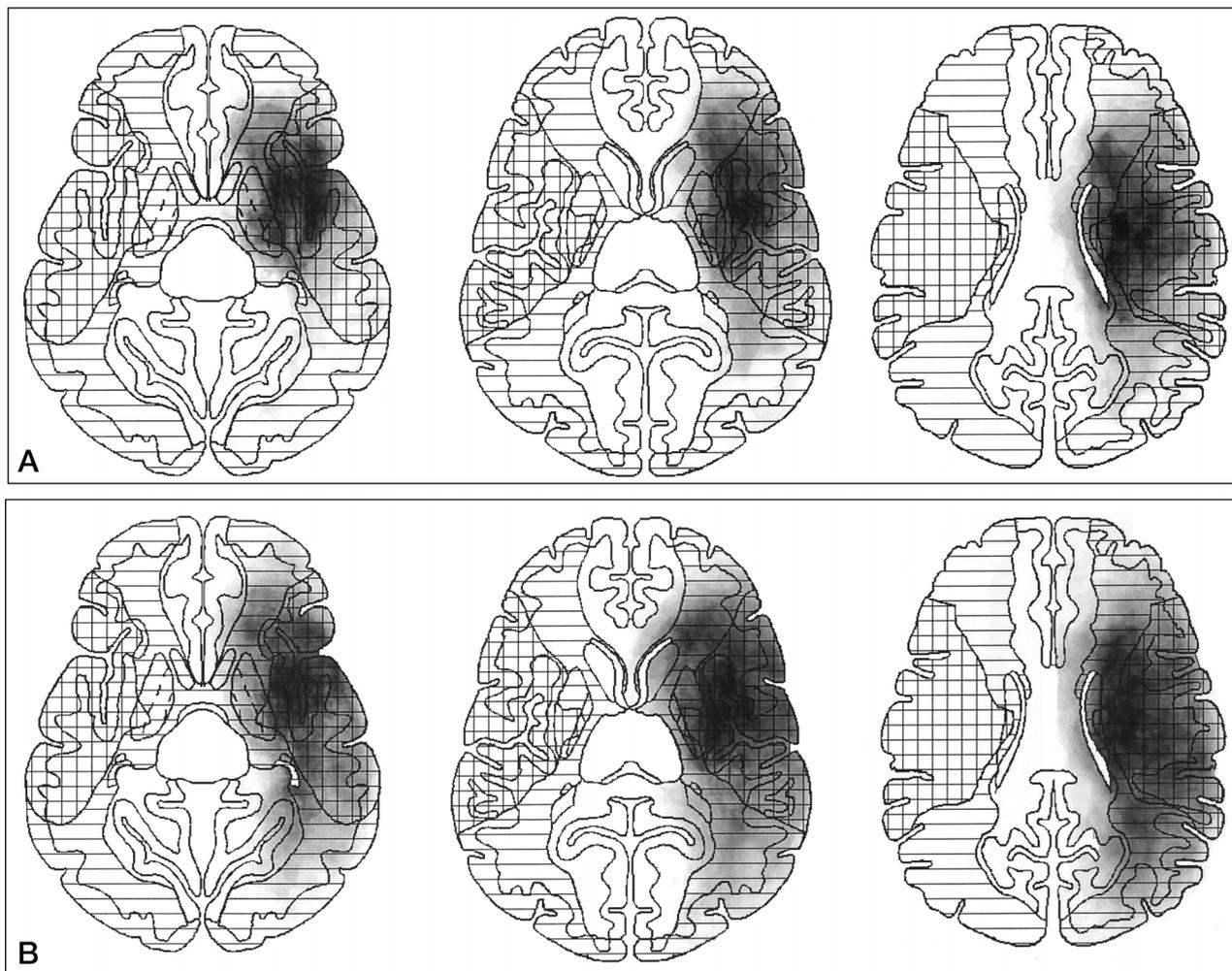
* $P < .05$.

FIG 3. Graphic representation of cortical infarcts in patients with carotid obstructions (high-grade ICA stenosis) (A) and nonvalvular atrial fibrillation (cardiac source of embolism) (B) superimposed, in the composite image, onto the territorial extension map (ventricular, basal ganglia, and thalamic levels) according to van der Zwan et al [16].

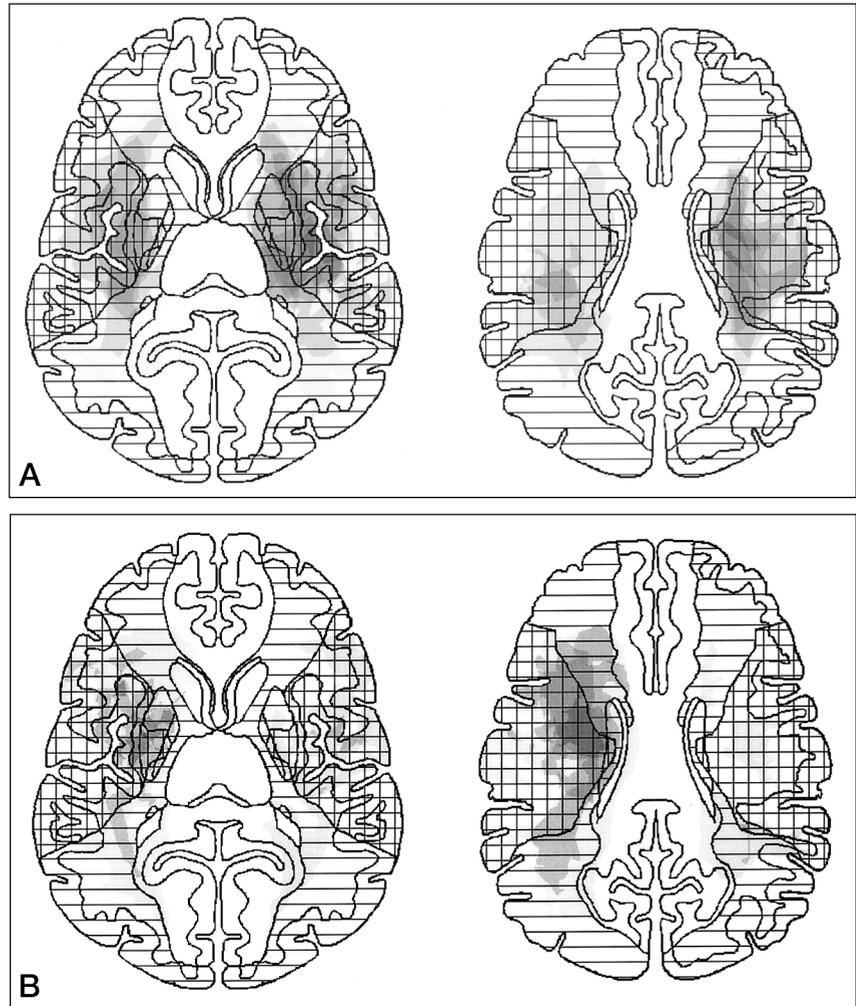
seem to support this interpretation of their findings (32, 33).

So far it is unclear exactly where cerebrovascular borderzones are located in individual patients. According to the demonstrated variability of the territorial blood supply (15, 16), only two types of brain infarcts can be distinguished with reasonable certainty: superficial territorial infarcts of either cardiac or artery-to-artery embolism and subcortical infarcts of heterogeneous origin. Some of these events might have resulted from borderzone infarcts, as reported

by Weiller et al (34), who identified 17 patients with "low-flow infarcts" distal to carotid occlusion and severely decreased cerebral perfusion reserve at single-photon emission CT. Others may result from overlapping subcortical territorial infarcts due to multiple artery-to-artery and cardiac embolism or even to small-vessel disease.

Our data from a recent multicenter acute stroke trial (NEST) and standardized analysis of the affected vascular territories in patients with clearly different sources of stroke confirm preliminary observations

FIG 4. Graphic representation of subcortical borderzone infarcts in patients with carotid obstructions (vascular group) (A) and nonvalvular atrial fibrillation (cardiac group) (B) superimposed, in the composite image, onto the territorial extension map (ventricular and basal ganglia levels) according to van der Zwan et al [18].



from an earlier study (17) that extraterritorial borderzone infarction is extremely rare in unselected patients with acute stroke and certainly does not occur more often in patients with hemodynamic compromise due to carotid obstructive lesions than in those with a cardiac source of stroke. This supports previous and more recent observations from the European Carotid Surgery Trial (ECST) by Hupperts et al (18, 19), who also questioned this concept on the basis of variations in the topographic distribution of major cerebral arteries seen in postmortem studies (15, 16). However, data from the ECST study might have been less suitable to test the borderzone concept, as patients with carotid occlusion most likely to develop the “low-perfusion-syndrome” were excluded, and an overestimation of the hemodynamic relevance of mild/moderate degrees of carotid stenosis might have introduced further bias by leading to the evaluation of the local degree of stenosis rather than the distal one. In contrast, the surprisingly high prevalence of borderzone type infarcts, associated with ICA stenosis in their series, makes hemodynamic failure in distal/adjacent end-zone territories or even low-perfusion territories alone (ie, the leading concept of extraterritorial infarction) less likely; however, it supports our assumption of artery-to-artery embolism outside the

narrow-sided territories of the MCA in these symptomatic patients.

Recent diffusion-weighted imaging studies in patients with repeat transient ischemic attacks distal to severe carotid obstruction have shown preferential manifestation of multiple spot lesions in the subcortical end-zone territories sometimes melting together into diffuse “borderzone-like” white matter lesions. In some patients, so-called high-intensity transient signals were observed during transcranial Doppler monitoring that indeed might have represented microembolic events (33). It is likely that the frequent generation of such microemboli (seldom indicative of embolic events) is favored in low-flow territories such as exist distal to moderate/severe carotid stenosis. Multiple extraterritorial infarcts may thus mimic borderzone infarcts as a result of particles flying off active sources of embolism into the hypoperfused vascular territories.

Our observation of a stronger association between deep borderzone infarcts and hemodynamic compromise in proximal cerebral arteries is supported by the findings of Del Sette et al (35), who reported deep borderzone infarcts in about 25% of 413 patients with ischemic lesions and ipsilateral carotid stenosis, indistinguishable from hemodynamic compromise. How-

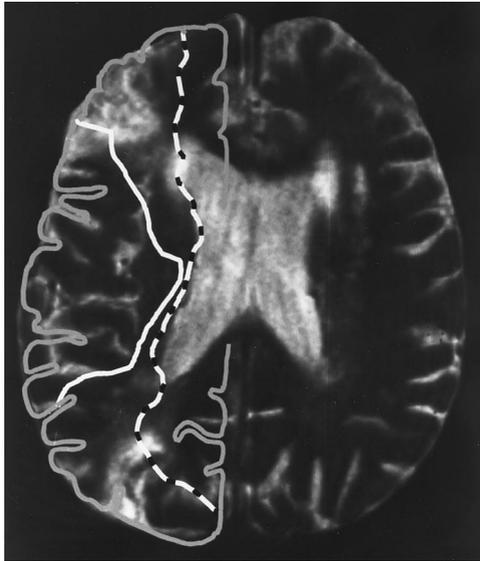


Fig 5. Superimposed drawing of a single ventricular level MR image in a patient with multiple cortical infarcts shows the inability to identify the underlying pathogenesis from the brain image. Assuming the smallest MCA territory (solid line), the anterior and posterior wedge-type infarcts are located in the large borderzone territories and could be attributable to a proximal carotid obstructive lesion. In contrast, assuming the largest MCA territory (broken line), both infarcts would represent territorial lesions probably resulting from simultaneous embolism or distal embolic fragmentation from an MCA stem occlusion.

ever, individual separation of both mechanisms by brain imaging alone is impossible, as no method is at present capable of identifying precisely tissue perfusion territories (ACA, MCA, PCA) *in vivo*. In addition, the other components claimed to play a substantial role in the concept of borderzone infarction have to be questioned. Hypoperfusion was often thought to be the cause of borderzone infarcts; however, documented cases are extremely rare and circumstances that seem to be associated with a high risk of systemic hypotension (eg, cardiac surgery) have not been proved to result in borderzone infarcts (31). Even if cases of superficial borderzone infarcts were analyzed selectively, no evidence has been found to support this particular theory (30–32, 35).

Conclusion

Decisions regarding the preferential use of thrombolytic agents in patients with different subtypes of acute stroke should not be based solely on CT or MR evidence of territory distributions, or on clinical features alone, or on both, even though recent studies have used such criteria for retrospective data interpretation (1, 2, 5). The often overlapping mechanisms (in 30% to 50% of cases) make it imperative that extensive vascular diagnostic work-up be performed to prevent misidentifying the individual patient's acute stroke subtype. The use of topographic patterns alone is inadequate to accurately determine acute stroke subtype and underlying pathogenesis, regardless of the brain imaging technique applied.

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