Prevalence and Volume of Internal Border Zone Lesions in Patients With Impaired Cerebral Carbon Dioxide Vasomotor Reactivity

A Follow-up Study

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Background: The precise etiology of border zone infarcts is controversial. Hemodynamic impairment due to obstructive disease of the internal carotid artery (ICA) is suggested as a cause of border zone infarcts.

Objective: To investigate changes in prevalence and volume of ischemic border zone lesions over time in patients with occlusive disease of the ICA after 1 year of follow-up.

Design: Follow-up study.

Setting: Referral center.

Patients: Fifty-eight patients with an occlusion of the ICA were included. At baseline, ischemic lesions were classified on magnetic resonance imaging, and vasomotor reactivity was assessed with transcranial Doppler ultrasonography with carbon dioxide challenge.

Main Outcome Measures: Changes in prevalence and volume of ischemic lesions were monitored and were correlated with carbon dioxide reactivity at baseline.

Results: No significant changes in the prevalence of any infarct types were observed after 1 year of follow-up in the hemispheres ipsilateral or contralateral to the ICA occlusion. However, in hemispheres ipsilateral to an occluded ICA, we found an increase in mean volume of internal border zone infarcts \( (P = .002) \). In hemispheres with a low carbon dioxide reactivity, we found an increase in mean volume of internal border zone lesions after 1 year (carbon dioxide reactivity, \( \leq 18\% \), \( P = .02 \) and 19%-35%, \( P = .02 \)). These changes were not observed for external border zone lesions.

Conclusion: The association between impaired vasomotor reactivity and an increase in ischemic lesion volume in the internal border zone suggests a hemodynamic component.

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Methods

Any investigators have studied stroke patterns in patients with obstructive disease of the internal carotid artery (ICA).\(^1\)\(^-\)\(^4\) Patients with severe obstruction have a high prevalence of border zone lesions.\(^2\)\(^-\)\(^3\) These lesions can be divided into those in the external and internal border zones.\(^5\)\(^-\)\(^7\) Hemodynamic impairment due to obstructive disease of the ICA is suggested as a cause of border zone infarcts.\(^5\)\(^-\)\(^6\) Other studies,\(^4\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) however, did not find an association between border zone infarcts and hemodynamic impairment and reported that arterial embolism is responsible for ischemic lesions in arterial border zone territories. Recently, it was suggested that an impaired clearance of emboli and microemboli due to hypoperfusion in the border zone territories could also cause ischemic lesions.\(^11\) The divergence in the concept of border zone infarcts is partly based on the fact that the location of these territories may vary among patients.\(^12\) In addition, studies that investigated the concept of border zone infarcts in relation to hemodynamic impairment were cross-sectional and therefore not suited to demonstrate a causal association. Moreover, all studies reported prevalence of ischemic border zone lesions rather than size of the lesions, whereas the latter may be a more accurate method by which to express ischemic damage.

The aims of the present study were to investigate the changes in prevalence and volume of ischemic brain lesions in patients with unilateral or bilateral occlusion of the ICA during 1 year of follow-up and to correlate these changes with carbon dioxide reactivity at baseline.

Methods

One hundred seventeen consecutive patients with transient ischemic attack (n = 23), transient mon-
oculomotor blindness (n=24), or moderately disabling stroke (modified 
ranking grade, ≤3) (n=70) that was associated with an 
angioanatomically proven occlusion of the ICA were followed up for 1 year. 
To focus on possible consequences of hemodynamic im- 
patment, we excluded patients with recurrent cerebral ische-
mic events (transient ischemic attack, n=3 and hemispheric is-
chemic stroke, n=4) or who underwent an extracranial (carotid 
endarterectomy, n=22) or intracranial (extracranial intracranial 
bypass, n=16) operation. Patients with contralateral ICA steno-
sis (70%-99%) (n=7) were also excluded because of the poten-
tial source of embolism in this artery. Four patients died (myo-
cardial infarction, n=3 and intercerebral hemorrhage, n=1), 
and 1 patient had a retinal infarction. In 2 patients, the follow-up im-
aging scans were of insufficient quality for review. In total, 58 pa-
tients (unilateral ICA occlusion, n=40 and bilateral, n=18) were 
analyzed in this study. All patients received antithrombotic medica-
tion (low-dose aspirin in most patients), and risk factors were 
rigorously managed. Blood pressure was managed on an indi-
vidual basis because of critical cerebral perfusion in some pa-
tients. The institutional review board of the medical center ap-
proved the study protocol.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) studies were performed on 
a Philips Gyroscan (Philips Medical Systems, Best, the Neth-
erlands) operating at 1.5 T. The mean±SD time between symp-
toms and baseline MRI was 82±57 days. All patients had the 
same MRI protocol of the brain at baseline and approximately 
12 months later (mean±SD, 389±56 days). The MRI exami-
nation consisted of 19 sagittal T1-weighted scout images (time 
to repeat, 2200 milliseconds and echo time, 10 milliseconds), 
19 transversal and oblique proton-density–weighted images 
time to repeat, 2200 milliseconds and echo time, 9 milli-
seconds), and 19 transversal and oblique T2-weighted images (time 
to repeat, 2200 milliseconds and echo time, 100 milliseconds).

Infarcts were identified as hyperintense lesions on T2-
weighted MRI and were classified as (1) external border zone, (2) 
internal border zone, (3) cortical territorial, and (4) lacunar (di-
ameter, ≤10 mm). Proton-density scans were used to distin-
guish infarcts from dilated perivascular spaces. Special atten-
tion was paid to exclude wallerian degeneration and leukoaraiosis 
as part of the internal border zone infarcts. Two investigators 
(C.J.M.K. and L.J.K.) reviewed all scans independently. Discrep-
ancies between the 2 readers were reevaluated in a consensus 
meeting. In addition, lesion volumes were measured.

TRANSCRANIAL DOPPLER WITH CARBON DIOXIDE 
REACTIVITY MEASUREMENT

Transcranial Doppler ultrasonography with carbon dioxide re-
activity measurement in the middle cerebral artery was per-
formed at baseline (mean±SD time between symptoms and base-
line Doppler measurement, 82±57 days) and approximately 12 
months later (389±56 days) with a Multi-Dop X device (DWL, 
Sipplingen, Germany). In 5 patients, transcranial Doppler ul-
trasonography was not possible because no signal was ob-
tained due to the absence of a temporal window, hence, 10 hemi-
spheres were excluded.

To obtain normal values, we investigated 30 control sub-
jects (25 male) without cerebrovascular disease, with a mean±SD 
age of 59±10 years (range, 40-78 years). The mean±SD car-
bond reactivity for the controls was 52%±17%.

We categorized the hemispheres of the patients into 3 
groups comprising those with a baseline carbon dioxide vaso-
motor reactivity of (1) 18% or lower (n=39), (2) 19% to 35% 
(n=31), and (3) 36% or higher (n=36).

STATISTICAL ANALYSIS

We used χ² tests, corrected for continuity, to compare the in-
crease in prevalence of ischemic brain lesions during 1 year of 
follow-up. Differences in mean volume of ischemic lesions be-
tween baseline and follow-up were tested with paired t tests. To 
test whether there was a difference in baseline characteristics be-
tween the 3 groups categorized according to their baseline hemi-
spheric carbon dioxide reactivity, we used χ² tests, with correc-
tion for continuity. We used linear regression to evaluate a possible 
trend in an increase in mean volume of internal border zone le-
sions between baseline and follow-up, depending on the hemi-
spheric vasomotor reactivity. P<.05 was considered significant.

RESULTS

We found no significant increase in the prevalence of any 
infarct type after 1 year of follow-up in hemispheres ipsi-
lateral or contralateral to the occluded ICA (Table). 

Between baseline and follow-up, an increase was found in 
the mean±SE volume of internal border zone infarcts in the 
hemispheres ipsilateral to the ICA occlusion (1.33±0.31 vs 2.03±0.47 mL, P=.002). An example of lesion 
enlargement is demonstrated in Figure 1. No signifi-
cant change in volume was found for the external bor-
der zone infarcts (2.40±1.05 vs 3.22±1.25 mL, P=.15). 

The mean±SD carbon dioxide reactivity in all pa-
tients at baseline was 24%±19% and did not signifi-
cantly change after 1 year of follow-up (28%±19%). The 
mean hemispheric carbon dioxide reactivity of each sub-

Figure 1. Proton density–weighted magnetic resonance images of the brain 
of a patient with unilateral occlusion of the left internal carotid artery. A, 
Showing an internal border zone lesion in the left hemisphere. B, The same 
patient 1 year later, showing an increase in volume of the internal border 
zone lesion.
group after 1 year of follow-up was the same as the baseline carbon dioxide reactivity. No differences were found in baseline characteristics (age, sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking, myocardial infarction, and peripheral vascular disease) between patients in the 3 groups of carbon dioxide reactivities (≤18%, 19%-35%, and ≥36%).

Figure 2A shows an increase in prevalence (P = .02) of internal border zone infarcts in the group with a carbon dioxide reactivity of 18% or lower, but not in the other 2 groups. Figure 2B shows an increase in internal border zone infarct volume between baseline and follow-up in the groups with a carbon dioxide reactivity of 18% or lower (P = .02) and 19% to 35% (P = .02). For the third group with a relatively normal carbon dioxide reactivity, no significant increase in lesion volume was found. Figure 2C shows the mean increase in lesion size as a function of carbon dioxide reactivity at baseline. We found a significant trend (P = .03) for less lesion growth within 1 year in patients with a higher carbon dioxide reactivity at baseline. Similar measurements for the external border zone lesions showed no significant differences in prevalence (Figure 3A), volume (Figure 3B), or changes in lesion size (Figure 3C) between baseline and follow-up in any of the 3 groups.

**COMMENT**

This study shows that patients with obstructive ICA disease do not have a significant increase in prevalence of ischemic lesions in the hemispheres ipsilateral or contralateral to an ICA occlusion during 1 year of follow-up. However, we found a significant increase in mean volume of internal border zone lesions in the hemispheres ipsilateral to the ICA occlusion. In hemispheres with a low carbon dioxide reactivity, prevalence and volume of internal border zone infarcts increased during 1 year of follow-up, compared with hemispheres with a normal carbon dioxide reactivity. These changes were not observed for external border zone lesions.

In our study, none of the infarct types investigated showed a significant increase in prevalence, which is not unexpected as we included only patients without recurrent symptoms. Still, an 8% increase in new infarcts in internal border zone regions was observed. Because we excluded patients with recurrent symptoms, these new infarcts were all silent (ie, asymptomatic). This percentage is higher than the annual stroke rate of 4.5% in patients with ICA occlusion.15 The size of all of these new infarcts was small. Contrary to the unchanged prevalence of internal border zone lesions, we found an increase in mean volume of these lesions in the hemispheres ipsilateral to the ICA occlusion after 1 year. Several etiological mechanisms of border zone lesion growth have been proposed: (1) an ulcerated plaque in the ipsilateral common or external carotid artery,16,17 (2) the presence of stump emboli,18 and (3) the presence of a chronic poor hemodynamic status of the brain.9 However, the first 2 mechanisms are rarely found in patients with border zone infarcts.9
At first sight, it seems surprising that no change in prevalence of internal border zone lesions was observed after 1 year, whereas significant lesion growth was found. However, changes in prevalence would have been caused by changes in the subgroup of patients who did not have internal border zone lesions at baseline, whereas lesion growth was measured in the subgroup of patients who already had internal border zone lesions at baseline. The latter group is probably a subgroup with a more unfavorable hemodynamic status. The subgroup without border zone lesions at baseline likely has a better cerebral hemodynamic status; thus, it is less likely that new low flow infarcts occur within 1 year.

In the second part of our study, we found that hemispheres with a low carbon dioxide reactivity demonstrated a significant increase in prevalence and volume of internal border zone lesions after 1 year. In contrast, no changes in prevalence and volume were found for external border zone lesions. Internal[8,9,15] and external border zone areas have been described as vulnerable areas in the brain for low flow infarction. Cross-sectional studies[8,9,15] demonstrated an association between hemodynamic impairment and the prevalence of ischemic lesions in the internal border zone areas in patients with ICA occlusion.

In addition to infarcts in the internal border zones, external border zone infarcts are frequently seen in patients with ICA occlusion. The external border zone is a watershed area, characterized by numerous pial arteriole anastomoses. The internal border zone is supplied by the medullary penetrators from the pial-middle cerebral artery system and the deep perforating lenticulostriate branches of the middle cerebral artery, which is a no-man’s-land for arteriolar structures, as there are no anastomoses between the deep perforators and the white matter medullary arterioles. The anterior border zone may selectively be vulnerable to severe ICA stenosis, as the occluded ICA should provide the anterior cerebral artery and middle cerebral artery vascular territory. In our study, we did not find any significant changes in volume or prevalence of external border zone lesions during 1 year of follow-up. Our findings do not support a hemodynamic component for external border zone lesion growth, although hemodynamic factors might have played a role in the etiology of these lesions at the time of the baseline event. As patients were selected because they had no new events during follow-up, the absence of volume increase in the external border zones may reflect that these areas are more clinically relevant than the internal border zones. Another complicating factor in our analysis might be that the exact location of external border zone territories is unclear in the individual patient, because of the variation in location of the vascular territories of the major cerebral arteries. This may have resulted in an incidental misclassification.

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