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Measurement of Time-to-peak Parameter by Use of a New Standardization Method in Patients with Stenotic or Occlusive Disease of the Carotid Artery

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BACKGROUND AND PURPOSE: A quantitative, easily obtained measure of cerebral hemodynamics would be valuable in planning surgical or interventional therapy for patients with stenotic or occlusive disease of the carotid artery. We evaluated the recently introduced standardized time-to-peak variable (stdTTP), obtained with dynamic susceptibility contrast-enhanced MR (DSC-MR) imaging, in different states of stenotic/occlusive carotid artery disease.

METHODS: We examined 24 patients with unilateral, high-grade stenosis (85%–95%) of one internal carotid artery (ICA) and 10 patients with stenosis (85%–95%) of one ICA and occlusion of the contralateral ICA. Mean stdTTP was evaluated in the central vascular territories of the anterior, middle, and posterior cerebral arteries and the anterior and posterior border zones and compared with the mean stdTTP values from 36 cerebral hemispheres without hemodynamic impairment.

RESULTS: Patients showed no significant prolongation of stdTTP in the central vascular territories compared with the reference group, whereas significant prolongations of stdTTP were measured in the anterior and posterior border zones in patients with ICA disease (ANOVA, $P < .05$) and were most prominent in higher grades of carotid disease. Hemispheres with hemodynamic impairment always showed a stdTTP > 3.5 s in the border zones.

CONCLUSION: The StdTTP quantitatively describes the hemodynamic impairment in cerebral hemispheres supplied by a stenosed or occluded ICA. An stdTTP value of > 3.5 s, as has been postulated, seems to point out hemodynamic impairment.

Severe stenotic or occlusive carotid disease can significantly impair cerebral perfusion. Dynamic susceptibility contrast-enhanced MR (DSC-MR) imaging provides several parameters that characterize and quantify the hemodynamics of the brain (1–3). Among others, the time-to-peak (TTP) variable has been found to be sensitive for hemodynamic alterations of cerebral perfusion (4). An automatic, offset calculation procedure for TTP was introduced to obtain a quantitative, easily reproducible measure for TTP that also allows comparisons among different examinations. This method, which produces the standardized TTP (stdTTP), needs neither an input curve nor normalization of

data. Standardized TTP measures the delay between early and late brain perfusion, which, under normal conditions, reflects the run time from perfusion in the central parts of a vascular territory to perfusion in the related border zones. As a practical limit for stdTTP, values ≤ 3.5 s in border zones were postulated (5).

Conventional TTP is thought to reflect the pathways blood must take to reach tissue. With impaired cerebral perfusion, such as occurs with stenotic or occlusive carotid artery disease, conventional TTP has been shown to be prolonged (6). The ability of stdTTP to give a reliable measure of cerebral hemodynamics has not yet been assessed, although this easy-to-use, quantitative measure would be of great value for planning surgical or interventional therapy.

The aims of this study were to examine the sensitivity of stdTTP in patients with stenotic or occlusive disease of the internal carotid artery (ICA), to assess the practicability of the postulated limit for stdTTP in border zones of 3.5 s, and to determine whether a critical value exists for stdTTP in cerebral perfusion of hemodynamically compromised patients.

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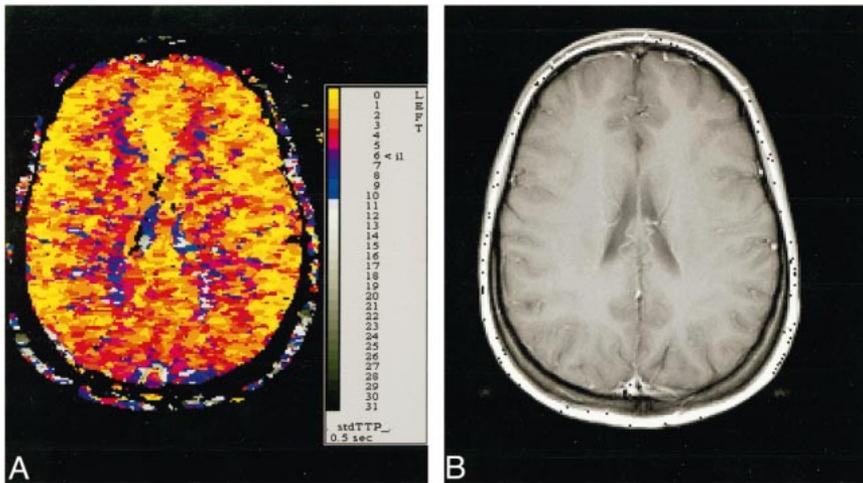


FIG 1. Patient without cerebrovascular disease or relevant hemodynamic alterations.

A, An stdTTP map obtained using DSC-MR imaging with a T2*-weighted echo-planar fast-field-echo sequence (74/30/1 [TR/TE/excitations]) with a 30° flip angle, a 240-mm field of view and a 128 × 128-voxel acquisition matrix. Central parts of vascular territories are displayed in yellow (time step 1, voxels with short stdTTP) and border zones in dark red (time step 5 and 6, voxels with long stdTTP) color. Each color step codes a time interval of 0.5 s.

B, Corresponding T1-weighted image (500/15/2) after IV administration of contrast medium.

Methods

Patients

Thirty-four consecutive patients underwent routine presurgical or preinterventional routine examination for symptomatic stenotic or occlusive carotid artery disease. All patients were outpatients and free of symptoms at the time of the MR examinations, but had suffered ischemic attacks previously. Informed consent was obtained in all cases.

Twenty-four patients had high-grade stenosis (85%–95%) of one ICA (Group 1, six women and 18 men aged 52–82 years). Of these, 19 patients had transitory ischemic symptoms ranging from slight paresthesia to mild hemiparesis referable to the hemisphere ipsilateral to the stenosed ICA; two patients had reported an amaurosis fugax, one ipsilateral to the stenosed ICA, the other with symptoms on both sides; two patients had had syncope; and one patient with high-grade stenosis of the left ICA presented with transient global amnesia.

Ten patients showed an occlusion of one ICA and a high-grade stenosis (85%–95%) of the contralateral ICA (Group 2, two women and eight men aged 52–77 years). Nine of these patients had presented with a mild hemiparesis referable to the hemisphere ipsilateral to the occluded ICA. In eight of these patients, the hand was affected most, whereas three patients also had slight facial paralysis. Another patient had had hypesthesia and mild paresis mainly of the leg. One patient had had only a short period of slight hypesthesia that mostly affected the right face and the right arm, which correlated with an occluded left ICA.

Grading of stenosis was performed according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (7). The results from 36 normal cerebral hemispheres, from patients without cerebrovascular disease, were pooled for comparison (Group 0, six women and 12 men aged 48–75 years) (Fig 1A and B).

MR Imaging

All patients underwent 3D phase-contrast MR angiography that depicted the complete vessel tract, from the bifurcations of the common carotid arteries up to the circle of Willis, and additional color-coded duplex sonography of the cervical vessel parts. Intraarterial digital subtraction angiography was available in all patients of group 2 and in eight patients of group 1. None of the patients had a significant stenosis or an occlusion in the vertebrobasilar system, or stenosis or hypoplasia of the proximal segments of the anterior (A1), the middle (M1), or the posterior (P1) cerebral arteries.

DSC-MR imaging was performed on a 1.5-T scanner (Gyrosan ACS-NT, Philips, The Netherlands) using a dynamic

multislice T2*-weighted echo-planar (EP) fast-field-echo sequence (74/30/1/30°/13 [TR/TE/excitation/flip angle/EP-factor]), a 240-mm field of view, and a 128 × 128-voxel acquisition matrix, and images were reconstructed within a matrix of 256 × 256 voxels. Two slices were measured with a slice thickness of 7 mm and a gap of 0.7 mm between the slices. The temporal resolution was approximately 365 ms (5). Scanning was performed in the axial plane at the level of the basal ganglia. During the examination, using an MR motor injector (Spectris, Medrad-Europe, The Netherlands), patients received a bolus injection of contrast medium (Gd-DTPA, 0.15 mmol/kg) through a 20-gauge cannula into a cubital vein, with an injection delay of 15 seconds and a flow rate of 8 mL/s. Morphologic imaging also included an axial fluid-attenuated inversion recovery sequence (7000/110/3 [TR/TE/excitations]) and a T1-weighted spin-echo sequence (500/15/2) before and after contrast medium administration.

Statistical Analysis

The data from the dynamic scan were transferred to a workstation and automatic masking and time leveling were performed to exclude voxels outside the brain parenchyma from further calculations. We calculated StdTTP maps using a 3% time offset, in which the TTP values of all voxels were rescaled relative to the time point when the first 3% of the evaluated voxels in a slice had reached their maximum enhancement (5).

The hemispheres were assessed in all groups as follows. The central vascular territories (CVTs) of the anterior, middle, and posterior arteries were defined as the voxels with the shortest stdTTP values (time steps 1 and 2) in the areas of an expected CVT. This definition includes a significant contribution by major branches of the feeding arteries to the stdTTP values of CVTs. In the same way, the anterior and posterior border zones were differentiated as voxels with the longest stdTTP in or adjacent to the expected areas of the border zones. This definition therefore includes mainly voxels representing dynamic curves from small or capillary vessels of the so-called “last meadows” of a territory. Obvious “shifts” of the expected border zone area to or from one of the adjacent CVTs were interpreted either as the preexistent individual situation or as a reaction to pathologic hemodynamics and, therefore, the measurements were taken at the “shifted” position. For border zones, only voxels with an stdTTP > 3.2 s were accepted, taking the proposed limit of 3.5 s in border zones of normal hemodynamic activity into account (5). Following these definitions, we measured the stdTTP in CVTs and border zones

FIG 2. Patient with high-grade stenosis of the left ICA.

A, An stdTTP map obtained using DSC-MR imaging with a T2*-weighted echo-planar fast-field-echo sequence (74/30/1 [TR/TE/excitations]) with a 30° flip angle, a 240-mm field of view and 128 × 128-voxel acquisition matrix. Each color step codes a time interval of 0.5 s. The left hemisphere still shows a small region of normal perfusion within the CVTs (*yellow voxels*). In the anterior and posterior border zones, stdTTP is significantly prolonged, visible as an increase of voxels shifting color from normally *dark red to blue* and *gray*. A slight prolongation of stdTTP in the anterior and posterior border zones in the right hemisphere (color shift to *magenta to blue*) was not significant.

B, Corresponding T1-weighted image (500/15/2) after IV administration of contrast medium.

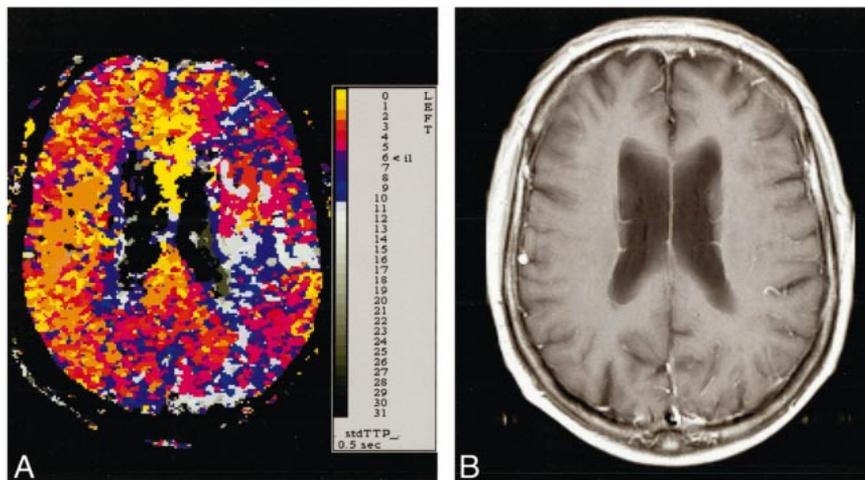
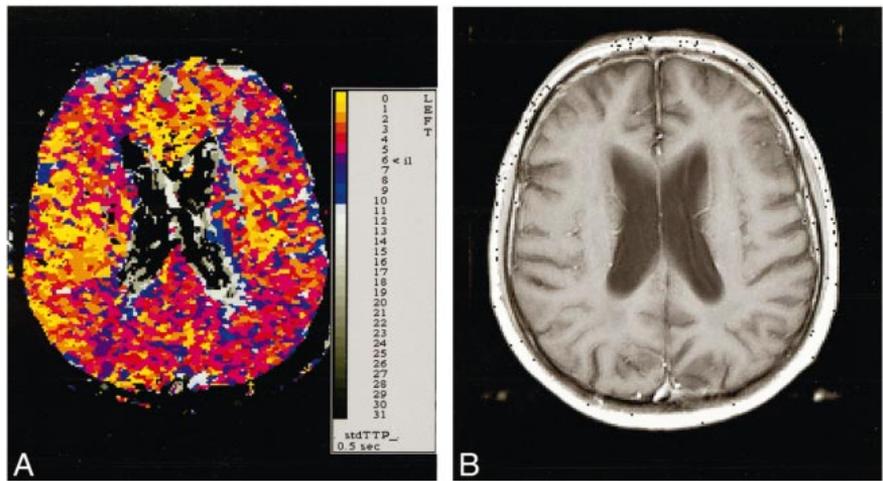


FIG 3. Patient with high-grade stenosis of the right ICA and occlusion of the left ICA.

A, An StdTTP map from DSC-MR imaging using a T2*-weighted echo-planar fast-field-echo sequence (74/30/1 [TR/TE/excitation]) with a 30° flip angle, a 240-mm field of view, and a 128 × 128-voxel acquisition matrix. Each color step codes a time interval of 0.5 s. In the left hemisphere, the stdTTP is markedly prolonged in the anterior and posterior border zones (shift from normal *dark red to gray*) and in the central territory of the middle cerebral artery (shift from normal *yellow to red or magenta*). The vascular territory adjacent to the central region shows a shift to *blue* and *gray* values comparable with that of border zones. This was interpreted as a result from atherosclerotic small vessel disease, because the morphologic examination showed no related lesion. On the right side, the stdTTP was moderately prolonged, shown as moderate increases in *magenta* and *blue* voxels in the border zones.

B, Corresponding T1-weighted image (500/15/2) after IV administration of contrast medium.

by using regions of interest with a mean size of 1.4 cm³. Areas exhibiting abnormal signal intensity on fluid-attenuated inversion recovery sequences were excluded.

For statistical evaluation, stdTTP was to be rationally scaled. We calculated descriptive statistics for stdTTP (the mean, its standard deviation, and a 95% confidence interval of mean). We compared groups by use of the ANOVA test with the Bonferroni correction and a significance level of .05.

Results

Morphology

In group 1, 14 patients showed small lacunar lesions, mainly affecting the basal ganglia. Two pa-

tients presented with chronic infarctions in the basal ganglia in the hemisphere ipsilateral to the stenosed ICA. In group 2, we found three small infarctions in the border zones, each in the hemisphere ipsilateral to the occluded ICA, and in one case, a pure subcortical type of hemodynamic infarction in the posterior border zone (8). The same patient manifested a cortical infarction in the anterior border zone of the hemisphere ipsilateral to the occluded ICA. Another patient in group 2 presented with cortical infarction in the posterior border zone. No patients in any group showed signs of acute or subacute infarction or disruption of the blood-brain barrier.

Hemodynamics

Identification of CVTs and of border zones on both sides was possible on all stdTTP maps. In group 1, the stdTTP in the anterior border zone in the hemisphere isolateral to the stenosed ICA was significantly longer than in anterior border zones of group 0 (control group) (Fig 2A and B). The stdTTP also was significantly longer in the anterior border zones in both hemispheres (one ICA occluded, the contralateral ICA stenosed) in group 2 patients compared with group 0 patients (Fig 3A and B). No significant difference was found between stdTTP in the anterior border zone of group 0 and the anterior border zone in the hemisphere supplied by the normal ICA in group 1. The same results were found in the posterior border zones of groups 1 and 2 compared with group 0.

The CVTs showed clearly different results. Among all three groups, there was no statistically significant difference in stdTTP for the CVTs of the anterior and posterior cerebral arteries. The stdTTP was significantly prolonged in the CVT of the middle cerebral artery (compared with that in group 0) only in hemispheres isolateral to the occluded ICA in group 2.

Descriptive statistics for each group are summarized in the Table and displayed in Figure 4A and B.

Discussion

DSC-MR imaging proved useful for the evaluation of acute stroke and stenotic or occlusive carotid or neurodegenerative disease (1, 4, 9, 10). Quantification of DSC-MR measurements is desirable to enable comparisons of measurements from different examinations. The TTP or peak enhancement parameter variable with DSC-MR is easy to access and was reported to be sensitive for the detection of hemodynamic impairment (4, 11, 12). To obtain quantitative measures for TTP, however, the introduction of an arterial input curve or normalization is necessary. An alternative has been introduced, the stdTTP, which also allows quantification with significantly fewer procedural efforts. The stdTTP uses an offset for standardization, calculated from the TTP of the first 3% of the evaluated voxels in a slice that reach their peak enhancement (5). In patients without cerebrovascular disease, stdTTP exhibited good reproducibility and comparability of the data from different examinations. Owing to the architecture of the cerebral vessel tree in a normal situation, very short stdTTP values—almost equal to the calculated offset—have been found in CVTs. For the same anatomic reason, the stdTTP in border zones was found to be longer than in CVTs in cerebrovascularly healthy subjects, and a limit of stdTTP ≤ 3.5 s in border zones has been postulated (5). However, the reliability of stdTTP to quantify hemodynamic alterations, the practicability of the proposed limit,

and the factors affecting stdTTP have not yet been analyzed in a pathologic cerebrovascular condition.

Our results clearly show that stdTTP in border zones increases significantly with higher grades of stenotic or occlusive carotid artery disease and that the proposed limit of 3.5 s for stdTTP in border zones is exceeded. In group 2, in which one ICA was highly stenosed and the other ICA was occluded, the stdTTPs in the border zones isolateral to the occluded ICA were almost twice the proposed normal value (1.7 times normal in the anterior border zone and 1.8 times normal in the posterior border zone). In comparison, the stdTTPs in border zones of hemispheres supplied by the stenosed ICA in group 2 exceeded the proposed normal value by approximately 1.4 times. This result almost matches the comparable situation in group 1, in which one hemisphere also was supplied by a high-grade stenosed ICA. The proposed normal limit was exceeded by approximately 1.3 times in border zones in the hemispheres isolateral to a high-grade ICA stenosis in group 1. Therefore, in hemispheres isolateral to an ICA with a high-grade stenosis, an stdTTP in border zones is significantly longer than normal. On the other hand, this prolongation clearly is smaller than that for stdTTPs measured in border zones in hemispheres isolateral to an occluded ICA. The stdTTPs in border zones of hemispheres supplied by a normal ICA did not differ significantly from the proposed normal value in group 1. The stdTTP values measured in border zones in these hemispheres did not exceed the proposed limit of 3.5 s.

From a morphologic point of view, lesions fulfilling criteria for hemodynamic infarction occurred only in hemispheres isolateral to an occluded ICA, for which the stdTTP in border zones was nearly double the proposed limit. This indicates that, in this population, cerebral perfusion could have been insufficient owing to hemodynamic factors (8). On the other hand, no such lesion was observed in hemispheres isolateral to a stenosed ICA, for which the stdTTP in border zones exceeded the proposed limit by not more than 1.5 times. A stenosed ICA therefore could represent a relatively lower hemodynamic risk for the isolateral hemisphere than an occluded ICA, a suggestion that is consistent with earlier reports regarding hemodynamic infarctions (13, 14). Although further research on this issue is necessary because of the small number of patients in group 2, the finding of an stdTTP value at least twice the proposed limit of 3.5 s with border zone infarctions is remarkable and may not be an incidental finding.

For CVTs, a significantly longer-than-normal stdTTP was found only in the territory of the middle cerebral artery isolateral to an occluded ICA. The longer path required for blood to reach the territory of the middle cerebral artery, as has been postulated for conventional TTP (6), may help explain this finding in this special scenario. This does not, however, explain the alterations of stdTTP in

StdTTP of patients with cerebrovascular disease

Group	Side	ACA-CVT StdTTP(sec)	a-BZ StdTTP(sec)	MCA-CVT StdTTP(sec)	p-BZ StdTTP(sec)	PCA-CVT StdTTP(sec)
Grp 0	ICA _{normal}	0.4 ± 0.08 0.2–0.5	2.3 ± 0.1 2.2–2.5	0.5 ± 0.05 0.4–0.6	2.8 ± 0.1 2.7–3.0	1.4 ± 0.1 1.3–1.6
Grp 1	ICA _{normal}	0.2 ± 0.08 0–0.4	2.4 ± 0.1 2.2–2.7	0.3 ± 0.1 0.1–0.4	3.0 ± 0.1 2.8–3.2	1.0 ± 0.1 0.8–1.3
	ICA _{sten}	0.2 ± 0.1 0–0.4	3.6 ± 0.2 3.2–4.1	1.2 ± 0.3 0.6–1.7	4.1 ± 0.3 3.6–4.6	1.3 ± 0.2 0.8–1.8
Grp 2	ICA _{sten}	0.7 ± 0.4 0–1.6	5.0 ± 0.3 4.2–5.7	0.8 ± 0.4 0.07–1.7	4.9 ± 0.5 3.8–5.9	1.2 ± 0.3 0.5–1.9
	ICA _{occ}	0.4 ± 0.3 0–1.0	6.3 ± 0.8 4.4–8.2	1.8 ± 0.8 0.03–3.7	5.8 ± 0.5 4.6–7.0	0.9 ± 0.3 0.2–1.5

Note.—CVT, central vascular territory; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; a-BZ, anterior BZ; p-BZ, posterior BZ. The values (unit: second) are displayed as mean ± standard error of mean and 95% confidence interval (min–max). In groups 1 and 2, major and minor affected sides, by occlusive ICA disease, were differentiated. Group 0 represents a control series containing patients without cerebrovascular disease and without hemodynamic relevant alterations.

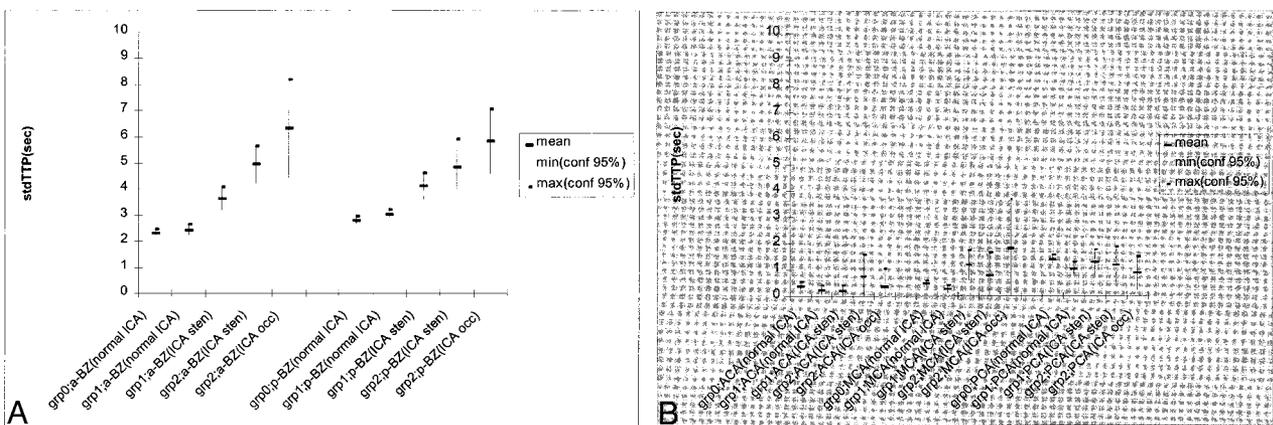


FIG 4. Mean stdTTP values with 95% confidence intervals (minimum to maximum).

A, Values measured in border zones. The stdTTP was not significantly prolonged in the anterior (a-BZ) and posterior (p-BZ) border zones in hemispheres supplied by a normal ICA in group 1 (grp 1; a-BZ and p-BZ [normal ICA]) compared with the control (grp 0; a-BZ and p-BZ [normal ICA]). All other groups showed significantly prolonged stdTTP values. In relation to a proposed limit of 3.5 s for the stdTTP value in border zones, this was moderate in hemispheres supplied by a highly stenosed ICA (grp 1; a-BZ and p-BZ [stenotic ICA]) and grp 2; a-BZ and p-BZ [stenotic ICA]), but severe in hemispheres ipsilateral to an occluded ICA (grp 2; a-BZ and p-BZ [occluded ICA]).

B, Values measured in the CVT of the anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries showed behavior completely different from that of border zones. Only in the CVT of the MCA in group 2 (grp 2; MCA [occluded ICA]), in whom the ipsilateral ICA was occluded and the contralateral ICA showed a high-grade stenosis, was the stdTTP significantly increased compared with the control group (grp 0).

the case of a high-grade stenosis of an ICA. In this case, the stdTTP in the border zones was significantly longer than normal, but the length of the path for the blood to reach the ipsilateral hemisphere does not change. Furthermore, despite the identical anatomy of the pathways to the hemispheres ipsilateral to a high-grade stenosis of an ICA in groups 1 and 2, the stdTTP always was longer in for the comparable border zones in group 2. According to Hagen-Poiseuille's law, longer pathways with smaller vessel diameters in the primary collaterals, as well as an eventually reduced perfusion pressure in a feeding vessel, will reduce the flow rate. Reduced flow rates can induce lower gradients of the dynamic curves, which in consequence lead to longer stdTTPs. It is obvious that reduced flow rate has a greater impact on slowly

perfused, small vessels on the periphery of a vascular territory than on the more quickly perfused central vessels.

Because of how regions of interest were defined in this study, we measured the stdTTP primarily from the rapidly perfused, central sections of the vascular for CVT, but the regions of interest in the border zones recorded the stdTTP from more peripheral, small vessels with normally lower flow rates. In hemispheres ipsilateral to a stenosed ICA, then, the border zones may show significantly prolonged stdTTPs when no significant prolongation of stdTTP is measureable in CVTs. On the other hand, a measureable, significant prolongation of stdTTP in a CVT most likely is in the territory of a middle cerebral artery ipsilateral to an occluded ICA, because the hemodynamic impairment was

strongest in this situation compared with other CVTs in this study. Additionally, and in accordance with the effects of reducing flow rate in border zones and CVTs, the longest stdTTP values were found in border zones adjacent to such CVTs.

Conclusion

Hemodynamic alterations of cerebral perfusion caused by carotid occlusive or stenotic disease is reliably detected and quantified by stdTTP. The proposed normal limit for stdTTP of 3.5 s was confirmed in this study. We hypothesize that doubling this value bears a high hemodynamic risk, and that prolongation of stdTTP reacts to flow rate reductions in CVTs and border zones in stenotic or occlusive carotid artery disease.

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