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Perfusion and molecular diffusion-weighted MR imaging of the brain: *In vivo* assessment of tissue alteration in cerebral ischemia

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Summary. The combined use of perfusion imaging (PI) and diffusion-weighted imaging (DWI) is opening a new window into the processes that occur during the first hours of ischemia. DWI detects changes in molecular diffusion associated with cytotoxic edema. PI characterizes the degree of regional hypoperfusion. Regions showing mismatches between DWI and PI, i.e. hypoperfused areas with normal diffusion behavior are considered potentially salvageable. We present results of 11 patients with an occlusion of the middle cerebral artery stem and spontaneous stroke evolution. Whereas the infarct was clearly visible on initial DWI and PI, surrounding tissue at risk of infarction was marked in all patients by an increased blood volume and transit time, but only in a subgroup (n = 3) where alteration were more pronounced this tissue at risk was progressively infarcted. These human DWI and PI data show alterations in the area of tissue at risk which correlates with infarct progression.

Keywords: Diffusion-weighted imaging – Perfusion imaging – Stroke – Brain – Penumbra

Introduction

Diffusion-weighted and perfusion MR imaging of acute stroke is shedding light on the complex mechanisms of acute ischemia (Baird et al., 1998; Darby et al., 1999; Keir et al., 2000; Oliveira-Filho et al., 2000). Diffusion-weighted imaging (DWI) detects the decreased mobility of water molecules associated with the development of cytotoxic edema in acute ischemia and displays affected brain areas hyperintens (van der Toorn et al., 1996). From the measured data an apparent diffusion coefficient (ADC) can be calculated. Contrarily to several animal studies, the measured decrease of the ADC in most human stroke studies was associated with irreversible cell damage (Baird et al., 2000; Fiehler et al., 2001; Flacke et al., 1998; Rordorf et al., 1998; Wu et al., 2001). This is likely related to the moderate diffusion weighting of these measurements. Reports of reversible ADC reduction in acute stroke are scarce (Doege et al., 2000; Oppenheim et al., 2000a; Wang et al., 1999).

Perfusion imaging (PI) measures MR signal alterations during the first pass of an injected contrast agent (Ostergaard et al., 1996, 1998). From these continuously registered data several semiquantitative perfusion related parameters can be derived in a straightforward matter.

Recent studies have emphasized the benefit of co-registration of both DWI and PI in the emergency assessment of acute stroke (Baird et al., 2000; Fiehler et al., 2001; Barber et al., 1998; Beaulieu et al., 1999; Karonen et al., 2000; Keller et al., 1999; Schellinger et al., 1999; Tong et al., 1998). This co-registration allows identification of the infarct core where cytotoxic edema has already developed and simultaneously displays perfusion alterations of the surrounding area where cellular integrity is still maintained (Barber et al., 1998; Schlaug et al., 1999). This surrounding area of tissue at risk of infarction, the so-called penumbra, is the principle target of acute treatment. In case of thromboembolic vessel occlusion the amount of oxygen supply provided by collateral circulation is the key parameter that decides upon complete recovery or tissue necrosis in the areas compromised by the vessel occlusion (Sakoh et al., 2000). We hypothesized that the analysis of ADC and semiquantitative perfusion parameters not only allows the identification of the area of tissue at risk but may also allow to predict

whether this tissue will recover or not. The purpose of this study was to describe ADC and perfusion parameters in acute thromboembolic stroke and to derive criteria to predict final infarct extension. In order to include a homogeneous subset of patients with a well-defined pattern of occlusion we only included patients with an angiographically proven occlusion of the main stem of the middle cerebral artery and thus considering the entire MCA territory downstream the occlusion as tissue at risk of damage.

Material and methods

Subject population

Patients of this study were recruited from a larger cohort of patients prospectively imaged with MRI and CT within 6 hours after onset of hemiplegia or aphasia. Imaging was performed according to the guidelines of the local ethical committee. Inclusion criteria for study were: 1) an angiographically (digital subtraction angiography n = 5, magnetic resonance angiography n = 6) proven occlusion of the middle cerebral artery; 2) a spontaneous course of stroke under anti-coagulation therapy with heparine; 3) at least one follow-up examination within one week (7 ± 1 days) with MRI (n = 7) or CT (n = 11). All patients who received local or systemic thrombolytic therapy were excluded from this study. Initial clinical findings were scored according to the NIH-stroke scale (NIHSS), the clinical presentation at discharge was scored according to the modified Rankin scale (Goldstein et al., 1997; van Swieten et al., 1988). Eleven patients were successively enrolled into this study (Table 1).

MR imaging

All MR Imaging was performed at a 1.5T imager (Gyroscan NT; Philips Medical Systems, Best, The Netherlands). A standardized imaging protocol was used including T2-weighted GraSE imaging (TR/TE/α 3,520 ms/90 ms/90°; matrix 226 × 256; acquisition duration 0 : 53 min); time-of-flight magnetic resonance angiography (TR/TE/α 22 ms/2.8 ms/20°; matrix 196 × 256; acquisition duration 1 : 49 min); single shot echoplanar diffusion-weighted imaging (TR/TE/α 5,000 ms/85 ms/90°; matrix 92 × 128; acquisition duration 0 : 30 min) and 3D perfusion imaging (TR/TE/α 17 ms/26 ms/8°; matrix 64 × 64; acquisition duration 1 : 17 min) (Flacke et al., 2000). Diffusion-weighted images were acquired with b-values up to 1,000 s/mm^2 for three orthogonal direction of the diffusion gradients. ADC parameter maps for each direction of the diffusion gradient and for the trace of the diffusion tensor (ADC_t) were reconstructed from the data (Flacke et al., 1998; Murtz et al., 1998). Dynamic susceptibility weighted first pass perfusion imaging was performed after bolus injection of Gd-DTPA (Magnevist, Schering, Berlin, Germany) using the principles of echo-shifted acquisition (Flacke et al., 2000a; Liu et al., 1993). The bolus perfusion data were processed and converted into parameter maps of regional cerebral blood volume (rCBV), regional cerebral blood flow index (rCBFi), mean transit time (MTT), the time from injection to bolus peak (TTP), and time from injection to bolus arrival (T0) as previously described (Flacke et al., 2000b).

Data analysis

In a consensus reading of two experienced radiologists (S.F., H.U.) initial and follow-up infarct shape and size were assessed and grouped. The extension of initial hyperintensities on DWI, i.e. the regions where cytotoxic edema had already developed were compared to the extension of perfusion alteration on the various perfusion parameter maps.

The size of hyperintensities on initial DWI were considered to be a good estimate of initial infarct size. Therefore, this area was measured on the images with highest b-values using a segmentation software of an offline workstation (Easy Vision 4.0, Philips Medical Systems, Best, The Netherlands) and was compared to infarct size on follow-up examinations measured with the same methodology on T2-weighted GraSE or CT images.

Mean ADC_t were determined within regions of interest (ROI) of at least 40 pixels placed into the geometric center of the infarct on ADC_t parameter maps.

Under the assumption that in case of complete occlusion of the middle cerebral artery the entire territory fed by this artery downstream the occlusion is at risk of infarction we performed additional ROI measurements at different anatomic locations within the affected area on the various perfusion parameters maps. These measurements were performed in order to define: 1) regional differences of collateral blood supply in regions which were not infarcted on follow-up examinations and 2) to define initial perfusion parameters of regions which were progressively infarcted. After borders of the entire MCA territory were outlined according to Tatu and coworkers (Tatu et al., 1998), ROIs were placed in the insula, the anterior and posterior border zone and the periventricular and supraventricular white and gray matter. Larger vessels were excluded from the measurement by segmentation. By superimposing images of the final infarct extension on perfusion parameter maps it was guaranteed that no region which was progressively infarcted was included in the regions of interest. If necessary the 3D perfusion data set of the initial exam was reformatted to match the geometry of follow-up examinations. A second ROI measurement was performed in brain tissue which was not hyperintens (not infarcted) on initial DWI images but infarcted on follow-up examinations. To account for swelling of the entire brain due to vasogenic edema only larger tissue areas which are usually fed by a side branch of the middle cerebral artery were included into this analysis. For all measurements the ratio between the affected and a mirrored ROI placed into the identical area of the unaffected hemisphere was calculated.

Statistical methods

Measurements were expressed as means plus or minus the SD. The Pearson correlation coefficient was calculated to assess the correlation between initial ADC_t values and infarct size. Paired sample t-test was used to assess differences of perfusion measurements between the affected and unaffected hemisphere. All statistical tests were two-tailed, and all P values of less than .05 were considered to indicate statistical significance.

Results

Patient data, scores of clinical presentation, infarct location, infarct size and time of the initial imaging study of the eleven patients included into this study are given in Table 1.

DWI of good image quality were acquired in all patients. Gross head motion during the bolus injection of the MRI contrast agent did not allow reconstruction of perfusion parameter maps in one patient with a

Table 1. Summary of patient data, clinical scores an infarct size measurements

Gender and age	ADC_t of the infarct on initial DWI [10^{-5} mm^2/s]	Volume of hyperintensity on initial DWI [ml]/time from onset to initial DWI [min]	Infarct location	NIHSS	Rankin score discharge	Increase of infarct volume
M, 70	65	27,5/330	Striatocapsular	12	4	29%
F, 18	67	7,1/255	Striatocapsular	9	0	20%
F, 38	71	6,6/240	Striatocapsular	8	2	17%
M, 62	65	52,0/250	Frontal MCA territory, Insula	16	3	27%
M, 72	78	21,7/105	Striatocapsular and parietal MCA territory	12	3	25%
M, 79	67	45,5/300	Striatocapsular and parietal MCA territory	6	6	**94%**
F, 32	68	18,6/135	Frontal MCA territory, Insula	12	3	**116%**
F, 51	62	45,1/90	Frontal MCA territory, Insula	17	3	**90%**
M, 70	53	275,0/300	Complete MCA territory	23	6	15%
M, 56	45	287,6/330	Complete MCA territory	11	6	14%
M, 65	57	172,1/300	Complete MCA territory	20	6	13%

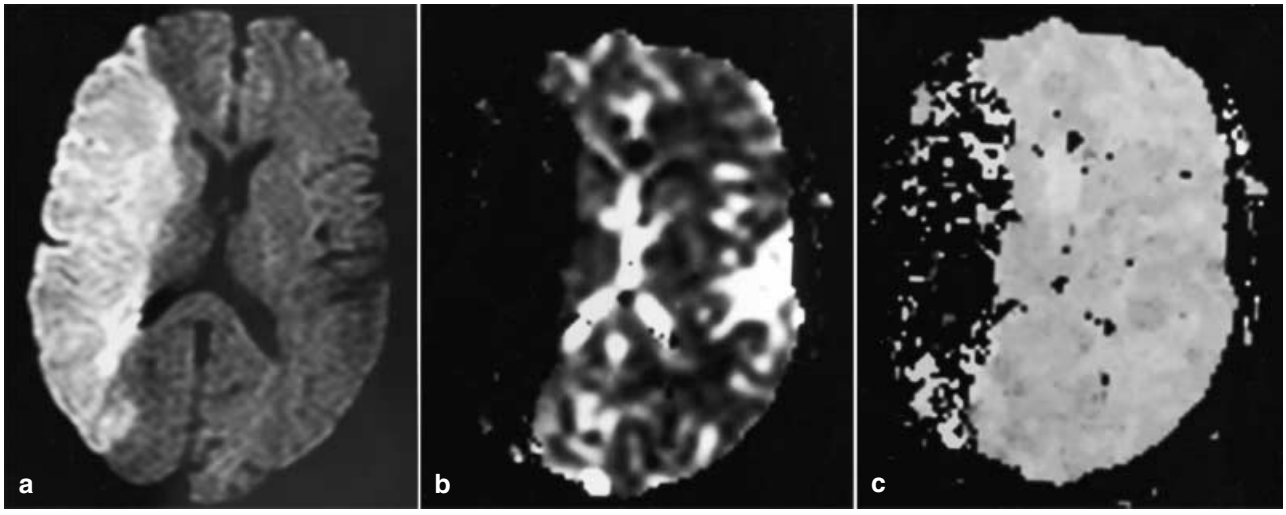

Fig. 1. 56-Year old patient with acute left sided hemiplegia for about 300 minutes. At the time of imaging the entire area of the right middle cerebral artery was already infarcted. The entire MCA territory was hyperintens on DWI (**a**) and the perfusion deficit on rCBV (**b**) and TTP (**c**) parameter maps matched the infarct area on DWI

complete infarct of the MCA territory. However, single pixel analysis showed no signal decrease during the passage of the contrast agent in the affected MCA territory, which was interpreted as a complete perfusion deficit.

There were three different image presentations:

complete infarcts of the MCA territory (n = 3) which were already hyperintens on initial DWI and had a complete perfusion deficit (Fig. 1)

striatocapsular infarcts (n = 3) with good collateral blood supply and no infarction of the cortex in the MCA territory on initial and follow-up examinations (Fig. 2)

cortical MCA infarcts (n = 5) with minor (n = 2) or substantial (n = 3) infarct growth (Fig. 3).

The mean infarct volume ranged from 6.6 to 288 ml. We observed an increased infarct volume at follow-up examination in all patients, due to infarct growth and

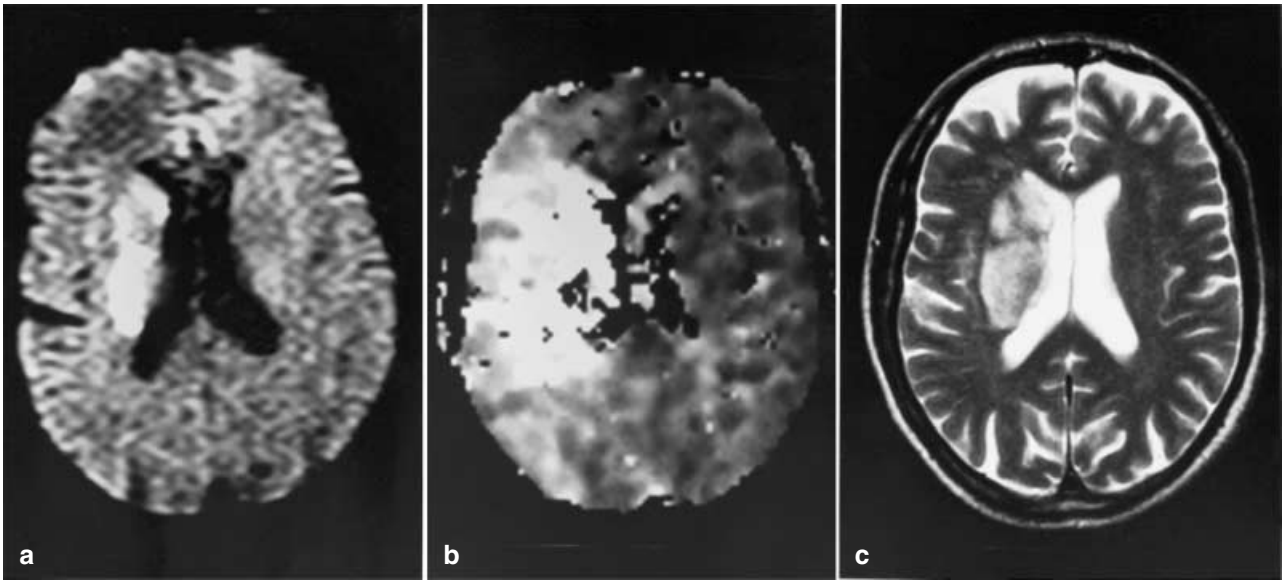

Fig. 2. 70-Year old patient with acute left sided hemiplegia for about 300 minutes. On initial DWI an enlarge striatocapsular infarct can be detected. On corresponding perfusion parameter maps of the initial imaging study there is an rCBV reduction and severe TTP delay within the hyperintens area of DWI (**a**) but there is also a remarkable delay of the TTP in the remaining territory of the occluded MCA (**b**). However collateral blood supply was sufficient in these areas such as no significant infarct growth was observed. On follow-up examinations (day 5), the infarct was still limited to the same striatocapsular region (**c**)

brain swelling. However, only in three patients there was a substantial infarct growth (more than 30%) exceeding the initial area of reduced regional cerebral blood volume and prolonged mean transit time (Table 1). The calculated ADC_t-values tended to be more reduced in larger infarcts ($r = -0.898$, $p < .01$).

The regional cerebral blood volume was reduced in the center of the initial infarct as displayed on DWI. The size of the area of reduced rCBV exactly matched the size of hyperintensity on DWI in all but three patients. In these three patients the area of reduced rCBV exceeded the hyperintens area on initial DWI by a small rim but matched the final infarct extension on follow-up examination. In these three patients (patient 1, 4 and 5) we observed a moderate growth of the infarct of more than 20%, if the hyperintens areas on initial DWI were considered to represent initial infarct extension.

Increased rCBV was observed in the area surrounding the rCBV reduction, with the exemption of the anterior border zone (Table 2). The mean transit time, the time to bolus peak, and the time of bolus arrival were increased in large areas of the MCA territory downstream the occlusion compared to the contralateral unaffected hemisphere where the measurements yielded: MTT = 9.3 ± 2.1 s, TTP = 27.8 ± 3.5 s and T0 = 22.3 ± 3.2 s. Time delays were slightly larger in the basal parts of the affected MCA territory (the insula and temporal cortex) than in the border zones towards the territory of the anterior or posterior cerebral artery (Table 2).

In three patients (6–8) where we observed a substantial infarct growth the tissue at risk which was progressively infarcted was neither hyperintens on initial DWI nor had a reduced rCBV on initial PI. The measured perfusion parameters of the progressively infacrted tissue at risk showed similar changes of perfusion parameters than the tissue at risk which was not infarcted on follow-up. The rCBV was increased and the mean transit time was prolonged resulting in a reduced rCBFi. Time of bolus arrival, and time of bolus peak were also prolonged. However, changes of the progressively infarcted regions were more severe on initial PI than those of areas, which were spared from infarction (Table 2).

Discussion

Roughly 80% of ischemic stroke are caused by thromboembolic occlusion of one of the major cerebral vessels. However, the extent of brain damage as a result of inadequate perfusion is usually smaller than the extent of the affected vessel territory. During the acute phase of ischemia the amount of remaining perfusion

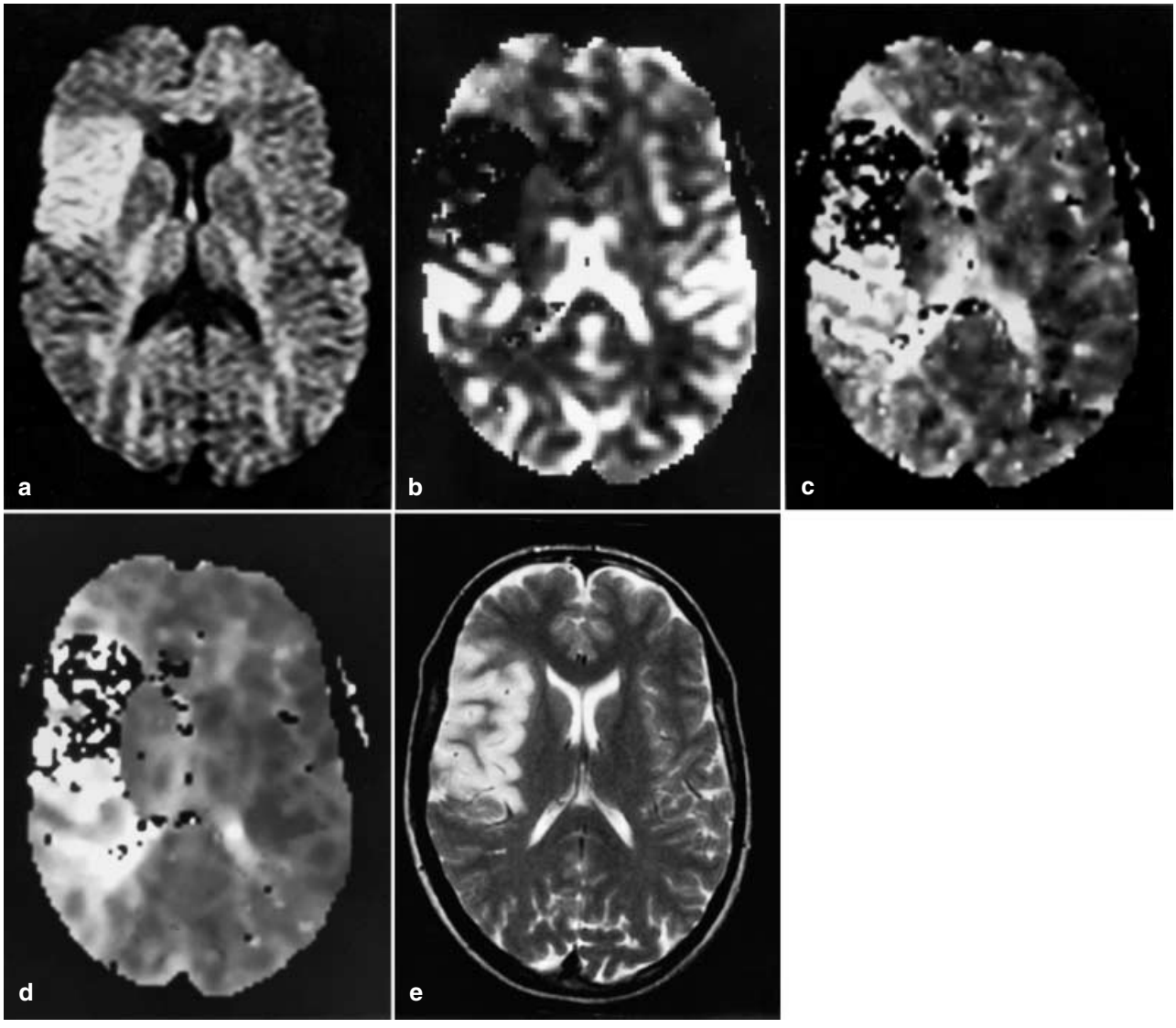

Fig. 3. 32-Year old patient with left sided hemiplegia since 120 minutes. Initial DWI (**a**) already show a partial MCA infarction. Correspondingly, initial perfusion parameter maps (**b–d**) show a perfusion deficit in the infarcted area. The surrounding area was marked by an increased rCBV (**b**) and a significant delay on MTT (**c**) and TTP (**d**) maps. On first follow-up examination (**e**) 24 hours later, the infarct had already grown into these areas

is the key parameter which influences maintenance of basic plasma membrane function (Sakoh et al., 2000). Surrounding the infarct core there is an area that is characterized by the loss of electrical activity as a consequence of ischemia but energy and oxygen supply is still sufficient to maintain ion homeostasis (Schlaug et al., 1999). Initially it is unclear whether this area can completely recover cellular function or will loose cellular integrity. This area described as penumbra is the principle target of thrombolytic and protective therapy in acute stroke. Diagnostic imaging aims to delineate this area and to predict its outcome.

Despite promising experimental results it is still not possible to fully characterize this penumbra by diffusion-weighted imaging alone (Fiehler et al., 2001; Schlaug et al., 1999). Several studies have emphasized the potential of DWI to detect cytotoxic edema associated with the disruption of ion homeostasis as an early marker of irreversible cell damage (Darby et al., 1999; Keir et al., 2000; Flacke et al., 1998; Barber et al., 1998; Karonen et al., 2000; Schellinger et al., 2001). However, the extent of hemodynamic changes in acute thromboembolism can only be sufficiently characterized if DWI is combined with PI. There is evidence

Table 2. Perfusion data of tissue at risk spared from infarction and tissue at risk which is progressively infarcted. The ratio between a ROI of the affected hemisphere and a mirrored ROI of the unaffected contralateral hemisphere was calculated for the different anatomic locations. Values are given as mean plus or minus the SD. Significant side differences are printed in bold letters. In addition the rank of the measurements for the different anatomical locations was considered. If a measurement was higher (lower) in more than 2/3 of measurements compared to the unaffected hemisphere the measurement was considered as increased (decreased) as indicated by the arrows. For comparison ratios of initial perfusion measurements of those areas which were progressively infarcted during one week of follow-up are listed

Anatomical region	rCBV	rCBFi	MTT	T0	TTP
Supratentorial gray and white matter (n = 8)	↑	±0	↑	↑	↑
	1.21 ± 0.24	0.97 ± 0.29	**1.18 ± 0.18**	1.05 ± 0.06	**1.10 ± 0.08**
	P = .093	P = .721	**P = .017**	P = .071	**P = .017**
Anterior borderzone (n = 7)	↓	↓	↑	↑	↑
	0.82 ± 0.09	0.89 ± 0.15	1.07 ± 0.13	1.03 ± 0.05	1.03 ± 0.05
	P = .002	P = .109	P = .183	P = .150	P = .202
Posterior borderzone (n = 8)	±0	±0	↑	↑	↑
	1.14 ± 0.27	0.95 ± 0.11	**1.20 ± 0.22**	1.07 ± 0.12	**1.09 ± 0.06**
	P = .286	P = .249	**P = .041**	P = .268	**P = .006**
Periventricular gray and white matter (n = 6)	↑	±0	↑	↑	↑
	1.44 ± 0.37	0.95 ± 0.34	**1.43 ± 0.26**	**1.12 ± 0.08**	**1.15 ± 0.08**
	P = .023	P = .568	**P = .004**	**P = .010**	**P = .006**
Insula (n = 7)	↑	↓	↑	↑	↑
	1.12 ± 0.24	**0.85 ± 0.10**	**1.39 ± 0.25**	1.20 ± 0.14	**1.21 ± 0.16**
	P = .346	**P = .001**	**P = .018**	P = .055	**P = .048**
Progressively infarcted Tissue at risk (n = 3)	2.17 ± 0.59	0.77 ± 0.16	1.67 ± 0.22	1.28 ± 0.08	1.32 ± 0.11

↑ = increased value, ↓ = decreased value, ±0 = no change
rCBV, regional cerebral blood volume; *MTT*, mean transit tiem; *rCBFi*, regional cerebral blood flow index (ratio of rCBV and MTT); *T0*, time of bolus arrival; *TTP*, time to bolus peak

that the magnitude of ADC reduction correlates with the severity of perfusion alteration (Fiehler et al., 2001), which is in agreement with the lower ADCt values measured in large and complete MCA infarcts in this study. Whereas infarcted tissue already appears bright on DWI, the surrounding area with sufficient blood supply to maintain basic cellular function has only moderate or no reduction of the ADC and remains undetected on visual analysis of DWI. However, this area usually demonstrates substantial changes on perfusion parameter maps according to the underlying collateral blood supply. The longer delay on T0 and TTP parameter maps in the basal part of the affected territory in our patients (the insula and the temporal lobe) may be related to the fact, that the collateral pathway towards these areas is longer than in the border zones of the MCA territory. From the mismatch of DWI and PI the extension of the tissue at risk of infarction and the severity of ischemia can be estimated (Darby et al., 1999; Schellinger et al., 2001; Oppenheim et al., 2000b). Currently, there is no unanimity which perfusion parameter is the best marker for perfusion alteration in acute stroke. Rordorf and coworkers observed an infarct growth into areas of reduced rCBV, similar to the observation made in this study for moderate infarct growth (Rordorf et al., 1998). The observed mismatch between the hyperintensities on DWI and the perfusion reduction is likely due to a short time delay between hyperintensities depicted and DWI and the underlying cellular mechanism (Flacke et al., 1999; Schwamm et al., 1998). An infarct growth was also reported if a mismatch between altered MTT parameter maps and initial hyperintense areas on DWI was observed. Tong and coworkers found a close correlation between infarct growth and the size of the area with prolonged TTP (Tong et al., 1998). Others only observed a close correlation between infarct growth and alterations on TTP maps if a threshold of 6 seconds time difference between affected and unaffected hemisphere was exceeded (Neumann-Haefelin et al., 1999). The results of this study underline that simple visual inspection of perfusion parameters may not be sufficient to predict further infarct growth. Tissue at risk of infarction that recovered showed similar but less severe alteration of the various perfusion parameters analyzed than tissue

that was finally included into the infarct. The observed increase of the rCBV in the area surrounding the infarct can be explained by the autoregulatory control of small arteries which increase the blood volume by reducing their resistance in order to compensate the reduced perfusion pressure. Increased blood volume in areas of prolonged mean transit time is a characteristic finding of brain regions fed solely supplied by collateral vessels on positron emission tomography. The potential of autoregulatory control may be exceeded in those areas with maximal rCBV increase and MTT and TTP delay. However, the continuous reduction of perfusion pressure cannot be sufficiently registered in the momentarily picture of an emergency MRI study. Nevertheless, regions with rCBV and rCBFi reduction can be readily identified and they likely represent areas where tolerable perfusion threshold could not be maintained. The observed reduction of the rCBV at the anterior border zone may be caused by a steal phenomenon, however at this point in time we cannot present sufficient data to prove this assumption.

Although discrimination between the tissue at risk which recovers and tissue at risk which will be infarcted is difficult and will require analysis of receiver operating characteristics on larger patient cohorts, the presented data already show a trend. E.g. if we consider TTP maps, the ratio between the affected and unaffected hemisphere amounting to 1.21 at maximum for tissue at risk spared from infarction (see Table 2) and the measured mean time to bolus peak for the unaffected hemisphere of 27.8 s, a tolerable limit of TTP delay in areas of tissue at risk can be calculated to about 6 seconds. This result is in good agreement with observations of Neuman-Haefelin and coworkers (Neumann-Haefelin et al., 1999). Similarly, a tolerable upper limit for MTT and T0 can be calculated. Further studies have to show if these values may allow prediction of individual outcome in patients.

Study limitations

The major limitation of this study is the small group of patients that could be included into the analysis. We thought to clearly define the affected territory and focussed on main stem MCA occlusions only. Our data may therefore only indicate a trend. A second limitation is the lack of validation of the observed perfusion alteration by an independent measure such as positron emission tomography or single photon emission computed tomography (Ostergaard et al., 1996; Karonen et al., 2000). These techniques are not widely used in emergency settings and were not available for this study. Similarly, we currently do not perform absolute quantification of MRI perfusion measurements, which would be possible by deconvolving the measured time-intensity curves with the arterial input function.

In conclusion, the analysis of the ADC and perfusion parameter maps show alterations in the area of tissue at risk in a well-defined thromboembolic stroke which correlates with infarct progression. Based on this analysis, tolerable limits of perfusion alterations for the various semiquantitative perfusion parameters may be derived, but further validation is required.

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