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ORIGINAL COMMUNICATION

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Diffusion weighted imaging, apparent diffusion coefficient maps and stroke etiology

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Abstract *Objective* In acute ischemic stroke, the number and distribution of lesions on diffusion weighted imaging (DWI) have been shown to give clues to the underlying pathogenetic mechanisms. The objective of this study was to determine whether lesion features on DWI differ between stroke due to large artery atherosclerosis (LAA) and cardioembolism (CE), and to assess the role of apparent diffusion coefficient maps (ADC). *Methods* We retrospectively studied 83 consecutive patients with stroke caused by either LAA (n = 40) or cardioembolism (n = 43). DWI lesions were characterized by number, size, distribution (i. e. lesion pattern) and signal intensity on ADC maps. In part A, all hyperintense DWI lesions regardless of their ADC were compared. In part B, only hyperintense DWI lesions with hypointense appearance on ADC maps (i. e. acute lesions) were assessed. *Results* Part A: The frequency of multiple hyperintense DWI lesions (LAA: 28/40, CE: 21/43; $p < 0.05$) and the lesion number (LAA 4.7 ± 4.9; CE: 3.1 ± 4.7; $p = 0.01$) were higher in LAA-patients. Involvement of > 1 circulation (i. e. anterior plus posterior or bilateral anterior circulations) was present in 5 LAA-patients (13 %) and 4 CE-patients (9 %). Lesion size did not differ between LAA-stroke (35.1 ± 33.7 mm) and CE-stroke (35.4 ± 27.8 mm). Part B: Multiple hyperintense DWI lesions with low ADC occurred in 23/40 LAA-patients and in 15/43 CE-patients ($p < 0.05$). Lesions in > 1 circulation occurred only in CE-stroke (n = 3; 7 %) and never in LAA-stroke. *Conclusions* (1) Multiple ischemic lesions occur significantly more often in LAA-stroke than in CE-stroke. (2) ADC maps are important in the comparison of DWI lesion patterns; DWI lesions in > 1 circulation can only be assigned to a cardioembolic etiology if they appear hypointense on ADC maps.

Key words stroke · diffusion weighted imaging · atherosclerosis · cardioembolism

Introduction

Using diffusion weighted imaging (DWI), acute ischemic lesions can be detected earlier [14, 24, 25] and with higher sensitivity and specificity [12] than on conventional MRI. Apparent diffusion coefficient (ADC) maps allow the differentiation of acute from subacute and chronic ischemic lesions [17, 18, 23]. Acute lesions are characterized by hyperintense signal on DWI and hypointense signal on ADC maps.

Recent studies indicated a link between lesion characteristics on DWI and the underlying pathogenetic mechanisms of stroke [2, 3, 7, 8, 11, 13, 15, 21]. In these

reports, multiple lesions were associated with embolic stroke etiologies such as large artery atherosclerosis (LAA) and cardioembolism (CE). However, only a few studies directly compared LAA and CE [7, 8, 15]. Mostly, they were restricted to subgroups, i. e. patients with multiple infarcts [15] or patients with infratentorial strokes [7]. Furthermore, the significance of ADC maps in comparing different stroke etiologies has not been evaluated. Thus, lesion features of LAA-stroke and CE-stroke had yet to be compared using DWI and ADC maps, in an otherwise unselected population.

With these considerations in mind, we tested the following hypotheses: (1) Acute LAA-stroke differs from acute CE-stroke in number, size and distribution of DWI lesions. (2) ADC maps provide additional information which is important for the distinction of LAA-stroke and CE-stroke.

Subjects and methods

Patient selection and clinical assessment

We evaluated all consecutive patients with acute ischemic stroke who were admitted to our neurological clinic between May 1999 and April 2001. The standard diagnostic procedure in our stroke unit comprised urgent CT, doppler/duplex-sonography, chest radiograph and ECG in all patients. Multimodal MRI was performed in most patients. Further diagnostic studies were performed according to a stepwise algorithm:

1. If the clinical syndrome (according to OCSP [4]), sonography and imaging findings were compatible with symptomatic large artery disease and the patient's history, clinical examination, chest radiograph and ECG revealed no evidence for embolic heart disease, further cardiac evaluation (i. e. echocardiography) was not mandatory, but possible at the discretion of the treating neurologist. Digital subtraction angiography was performed if MRA and sonography findings were conflicting or in case of stenting. For diagnosis of stenosis > 50 % (cut-off according to TOAST [1]) we used sonography in most cases. For the extracranial internal carotid artery [5], the large intracranial cerebral arteries and the vertebrobasilar arteries [6], published criteria of stenosis were applied. 2. If sonography criteria for LAA were not fulfilled, embolic heart disease was searched for with transthoracal or transesophageal echocardiography and Holter-ECG. 3. If the cardiac evaluation revealed no medium or high risk [1] embolic source, and if stroke syndrome and risk factors were not conformable with small vessel disease, additional laboratory and imaging studies were performed to search for other etiologies.

From our prospectively ascertained stroke database, we identified 219 consecutive patients with ischemic stroke who were evaluated with MRI including DWI, between May 1999 and April 2001. Demographic data, date and time of symptom onset, and clinical stroke syndrome according to the Oxfordshire Community Stroke Project (OCSP) criteria [4] were assessed from the data base. Two stroke physicians (LHB and PAL) retrospectively determined the etiology of stroke in these patients according to TOAST-criteria [1], based on the complete diagnostic investigations including conventional neuroimaging (MRI or CT), but blinded to DWI findings. Patients were included in the present study if (1) the single etiology of stroke was either LAA or CE and (2) clinical MRI including DWI was performed within 7 days after stroke onset. Patients with TIA, unknown time of stroke onset, stroke etiologies other than LAA or CE, or multiple etiologies were excluded. Eighty-three patients met the study criteria, 40 with LAA-stroke and 43 with CE-stroke. Chest radiography, 12-lead-ECG and extra-/intracranial doppler-duplex-sonography were performed in all cases (n = 83). Most patients underwent echocardiography (transthoracal: n = 33, transesophageal: n = 36). Selected patients were evaluated with digital subtraction angiography (n = 15) and 24-hours-ECG (n = 21).

DWI

Study patients underwent clinical MRI including DWI within 50.0 ± 40.0 hours (median 36.0) after stroke onset. DWI was performed on a 1.5T MR imaging system (Siemens Magnetom Symphony, Erlangen, Germany) using a single shot, multi-slice spin-echo, echo-planar imaging (EPI) sequence. Diffusion gradients were applied in three orthogonal directions to generate isotropic DWI using the following parameters: TR/TE 4741/105 ms, field of view 230, matrix 128 x 128 mm, b-values 0, 500 and 1000 s/mm^2, thickness/gap 5/2 mm. Apparent diffusion coefficient (ADC) maps were generated using the following equation: ADC = -logarithm $(S_{b=1000}/S_{b=0})/b_{1000}$ with $S_{b=1000}$ indicating the signal intensity on isotropic DWI and $S_{b=0}$ that prior to the application of diffusion gradients.

A single, experienced observer (STE) analyzed the images blinded to the patients' clinical data. Number and vascular territories of all hyperintense DWI lesions were noted according to previously published templates [22]. Topographically separate DWI lesions were assumed when no continuity was detectable between lesions in one slice as well as in adjacent slices [7, 11, 19]. In each patient, the size of the largest DWI lesion was assessed by its largest axial diameter [19]. For each hyperintense DWI lesion, the signal intensity on the corresponding ADC-map was assessed. For the present study, hyperintense DWI lesions were defined acute if the ADC-signal was hypointense, subacute if it was isointense and chronic if it was hyperintense [23].

For the definition of lesion patterns, we discerned: a) the anterior (i. e. carotideal) circulation of each hemisphere and the posterior (i. e. vertebrobasilar) circulation; and b) the vascular territories of the different cerebral arteries. The anterior circulation comprises the territories of the anterior cerebral artery (ACA) and the middle cerebral artery (MCA) of one hemisphere; the posterior circulation comprises the territories of both posterior cerebral arteries (PCA) and the infratentorial arteries. The following vascular borderzones were assessed: between the ACA and MCA, between the MCA and PCA, between the ACA, MCA and PCA, and the internal borderzone between superficial and deep perforating arteries.

Modifying the classifications of previous DWI studies [8, 9, 15, 19, 20], we specified 6 patterns of ischemic lesions: (1) Single lesion ≤ 15 mm in diameter. (2) Single lesion > 15 mm in diameter. (3) Multiple lesions in 1 vascular territory (i. e. ACA, MCA, PCA or infratentorial), excluding borderzone areas. (4) Lesions in > 1 vascular territory, within the unilateral anterior or the posterior circulation, excluding borderzones (i. e. unilateral ACA and MCA; bilateral PCA; PCA and infratentorial). (5) Multiple lesions within the unilateral anterior or the posterior circulation, including at least one lesion in borderzone areas. (6) Lesions in anterior plus posterior circulations or bilateral anterior circulations.

In part A of the study, number, size and distribution of all hyperintense DWI lesions were compared between the two groups, irrespective of their appearance on ADC maps. In part B, the same comparisons were made for the subgroup of hyperintense DWI lesions with low ADC (i. e. only acute lesions).

Statistical analysis

Student's T-test for unpaired variables was used for comparisons between categorical and continuous, normally distributed variables (e. g. stroke etiology and lesion size). For comparisons between categorical and ordinal variables (e. g. stroke etiology and number of DWI lesions), Mann-Whitney U-test was performed. Fisher's exact test was used to compare categorical variables (e. g. stroke etiology and single

vs. multiple lesions). The association between the lesion number and stroke etiology was corrected for age, interval between stroke onset and DWI, hypertension and diabetes mellitus in a stepwise regression analysis (Poisson).

A value of $p < 0.05$ was considered statistically significant. Data are expressed as mean and standard deviation, unless specified otherwise.

Results

Patient characteristics

LAA-patients were slightly older than CE-patients (LAA: 65.4 ± 10.5 years, CE: 63.7 ± 15.0 years; p = 0.027). The prevalence of arterial hypertension (LAA 28/40, CE: 21/43; p = 0.041) and diabetes mellitus (LAA: 10/40, CE: 4/43; p = 0.052) was higher in the LAA-group. The time interval between stroke onset and DWI did not differ significantly (LAA: 56 ± 41 hours, median 39.5; CE: 44 ± 39 hours, median 31.0).

In the LAA-group, 14 patients had unilateral and 5 patients bilateral stenosis of the internal carotid artery (ICA). Unilateral and bilateral stenosis of the middle cerebral artery was found in 6 and 3 patients, respectively. 7 patients had stenosis of the vertebral artery and 2 patients stenosis of the basilar artery. Combined stenosis of the ICA and the vertebrobasilar system was present in 3 patients.

Demographic data and stroke syndromes are summarized in Table 1.

Table 1 Patient characteristics

	LAA	CE	p-value
Number of patients	40	43	
Mean age (years)	65.4 ± 10.5	63.7 ± 15.0	0.027
Male (n,%)	26 (65%)	27 (62.8%)	n. s.
Mean latency of MR-imaging to symptom onset (hours)	56.1 ± 41.0	44.4 ± 38.7	n. s.
Arterial hypertension (n,%)	28 (70%)	21 (48.8%)	0.041
Diabetes mellitus (n,%)	10 (25%)	4 (9.3%)	0.052
Stroke syndromes (n)			
LACS	2	5	–
PACS	20	15	–
TACS	7	8	–
POCS	11	15	–

LAA indicates large artery atherosclerosis; *CE* cardioembolism
Stroke syndromes according to the Oxfordshire Community Stroke Project (OCSP) criteria [4]: *LACS* indicates lacunar syndrome; *PACS* partial anterior circulation syndrome; *TACS* total anterior circulation syndrome; *POCS* posterior circulation syndrome
n. s. indicates not significant

Number of lesions, lesion size and etiology

(A) All hyperintense DWI lesions

DWI showed hyperintense lesions in 78 patients (94%). Multiple lesions occurred significantly more often in the LAA-group (28/40 patients, 70%) than in the CE-group (21/43 patients, 49%) (p = 0.041). The number of lesions was significantly higher in LAA-patients (4.7 ± 4.9) than in CE-patients (3.1 ± 4.7) (p = 0.011). The maximum axial diameters of the largest DWI lesions did not differ between groups (LAA: 35.1 ± 33.7 mm, CE: 35.4 ± 27.8 mm; p = 0.96).

(B) Hyperintense DWI lesions with low ADC

They were present in 69 patients (83%). As in part A of the study, the frequency of multiple lesions (LAA: 23/40 patients, 58%; CE: 15/43 patients, 35%) as well as the number of lesions (LAA: 3.2 ± 4.0, CE: 2.1 ± 2.7) were significantly higher in the LAA-group than in the CE-group (p = 0.032 and p = 0.036) (Table 2).

Poisson regression analysis

After correction for age, interval between stroke onset and DWI, hypertension and diabetes mellitus, the association between stroke etiology and number of DWI lesions remained significant in both part A and part B of the study (Table 3).

Lesion patterns and etiology

(A) All hyperintense DWI lesions

Pattern 5 (multiple lesions within the unilateral anterior or the posterior circulation, including borderzones) occurred more often in LAA patients (13/40, 33%) than in CE-patients (5/43, 12%) (p = 0.020). Lesions in > 1 circulation (pattern 6) were detected in 4 CE-patients (9%), and in 5 LAA-patients (13%). In all LAA-patients with this pattern, the additional hyperintense DWI lesions in the contralateral anterior circulation or the posterior circulation were clinically asymptomatic. They appeared isointense or hyperintense but never hypointense on ADC maps. The other lesion patterns did not show significant group associations (Table 2).

(B) Hyperintense DWI lesions with low ADC

Pattern 3 (multiple lesions in a single vascular territory, without involvement of borderzone areas) was significantly associated with LAA (LAA: 11/40 patients, 28%; CE: 4/43 patients, 9%; p = 0.030). Lesions in > 1 circulation occurred only in CE-stroke (n = 3; 7%) and never in

Table 2 DWI/ADC characteristics

	A. All hyperintense DWI lesions			B. Hyperintense DWI lesions with hypointense ADC-signal		
	LAA (n = 40)	CE (n = 43)	p-value	LAA (n = 40)	CE (n = 43)	p-value
Lesions (n patients, %)						
no lesion	1 (2.5)	4 (9.3)	n. s.	4 (10.0)	10 (23.3)	n. s.
single lesion	11 (27.5)	18 (41.9)	n. s.	13 (32.5)	18 (41.9)	n. s.
multiple lesions	28 (70.0)	21 (48.8)	0.041	23 (57.5)	15 (34.9)	0.032
Number of lesions	4.7±4.9	3.1±4.7	0.011	3.2±4.0	2.1±2.7	0.036
Diameter of largest lesion (mm)	35.1±33.7	35.4±27.8	n. s.	–	–	–
Lesion patterns (n patients)						
1. single lesion < 15 mm	5	5	n. s.	5	6	n. s.
2. single lesion > 15 mm	6	13	n. s.	8	12	n. s.
3. multiple lesions in single territory	9	9	n. s.	11	4	0.030
4. lesions in multiple territories	1	3	n. s.	1	2	n. s.
5. multiple lesions including borderzone territories	13	5	0.020	11	6	n. s.
6. lesions in different cerebral circulations	5	4	n. s.	0	3	–

LAA indicates large artery atherosclerosis; *CE* cardioembolism; *n. s.* indicates not significant

Table 3 Stepwise Poisson regression analysis (effect on lesion number)

Variable	A. Analysis of all hyperintense DWI lesions			B. Analysis of hyperintense DWI lesions with hypointense ADC		
	OR	95% CI	p-value	OR	95% CI	p-value
[1]Age (increase 10 years)	1.02	0.93–1.13	0.50	1.00	0.89–1.13	0.128
[2]Latency to MRI (increase 10h)	1.02	1.00–1.05	0.05	1.01	0.98–1.05	0.372
Art. Hypertension (yes vs. no)	0.64	0.49–0.82	0.02	0.55	0.40–0.75	0.009
Diabetes mellitus (yes vs. no)	1.46	1.11–1.91	< 0.001	1.82	1.32–2.49	< 0.001
CE vs. LAA	**1.49**	**1.18–1.89**	**< 0.001**	**1.57**	**1.18–2.09**	**0.002**

Stepwise Poisson regression analysis: the effect of stroke etiology (LAA vs. CE) on lesion number is corrected for all variables above. Variables are added sequentially. Odds ratios (OR), 95% confidence intervals (CI) and p-values (chi-square) refer to the effect on lesion number.
[1] Calculated per increase of 10 years; [2] calculated per increase of 10 hours

LAA-stroke. The other lesion patterns did not show significant group associations (Table 2).

Examples of pattern 3 and pattern 6 are given in Figs. 1 and 2, respectively.

Discussion

Our study showed that (1) multiple ischemic lesions occur more frequently in stroke due to large artery atherosclerosis (LAA) than in cardioembolic (CE) stroke and that the absolute lesion number is higher in LAA-patients. (2) LAA-stroke and CE-stroke do not differ in the size of the largest DWI lesions. (3) Specific DWI lesion patterns are associated with LAA and CE. (4) ADC maps are relevant in the distinction of DWI lesion patterns: hyperintense DWI lesions in the anterior plus posterior circulations or in the anterior circulations of both hemispheres can only be assigned to CE-stroke if they appear hypointense on ADC maps.

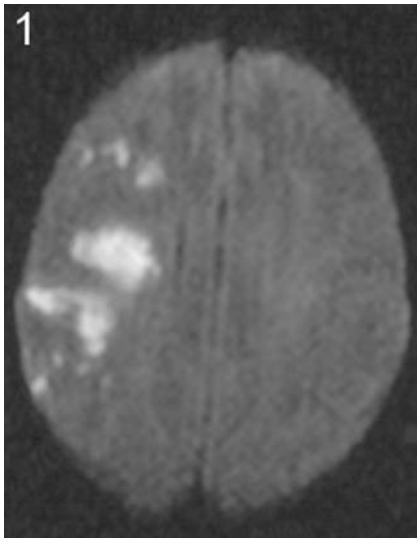

Fig. 1 Pattern 3: LAA-stroke (high grade stenosis of the right ICA): DWI shows multiple hyperintense lesions in the right MCA-territory

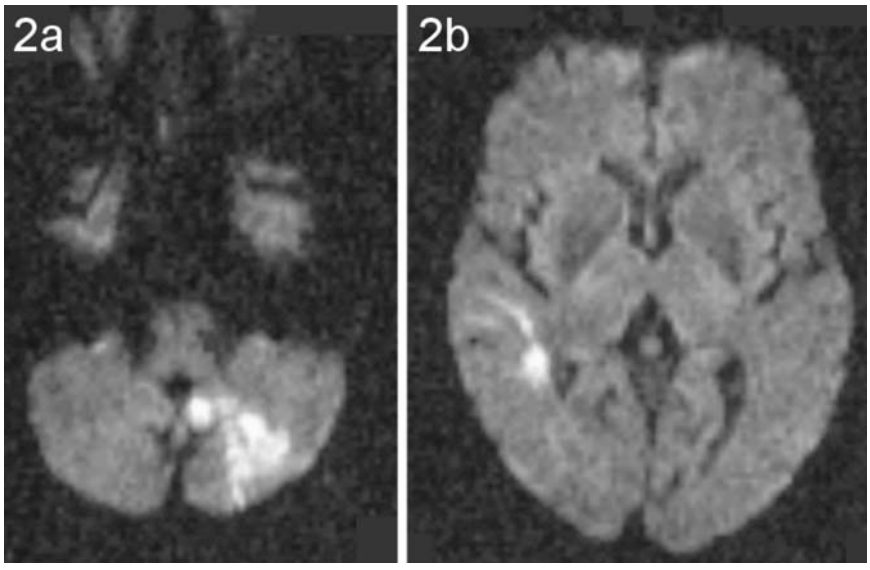

Fig. 2 Pattern 6: Cardioembolic stroke (atrial fibrillation): DWI shows hyperintense lesions in the posterior circulation (**2a:** left posterior inferior cerebellar artery) and in the right anterior circulation (**2b:** MCA-territory)

An association between the occurrence of multiple lesions on DWI and embolic stroke mechanisms of either arterial or cardiac origin has been reported before [2, 3, 7, 8, 11, 13, 15, 21]. However, DWI studies comparing both etiologies are rare. In a radiologically defined population of patients with multiple DWI lesions [15], LAA was more frequent than CE. Our study added the information that in a clinically defined population, the frequency of multiple DWI lesions as well as the number of lesions were significantly higher in LAA-stroke than in CE-stroke. This result held true regardless of whether all hyperintense DWI lesions or only those with low ADC (i. e. purely acute lesions) were considered.

The lesion signal on ADC maps, however, was important for the comparison of lesion patterns and etiology. This was most striking in the analysis of multiple DWI lesions in > 1 circulation (i. e. pattern 6). Such a pattern had been assumed to indicate CE-stroke [3, 7, 8, 19]. Our data showed that multiple DWI lesions in > 1 circulation occurred as often in LAA-stroke as in CE-stroke, if all DWI lesions were assessed, irrespective of their ADC. In contrast, if only DWI lesions with low ADC were considered (i. e. acute lesions), involvement of > 1 circulation occurred exclusively in CE-stroke and never in LAA-stroke.

The additional DWI lesions in distant circulations found in LAA-patients with pattern 6 were identified as subacute or chronic on the corresponding ADC-maps, and clinically did not contribute to the acute stroke syndrome. We therefore hypothesize that these lesions occurred before the index stroke. An unblinded post-hoc analysis revealed subsidiary potential mechanisms of ischemia in all those patients: asymptomatic contralateral ICA-stenosis (n = 1), aortic arch atherosclerosis < 4 mm (n = 1), and concomitant risk factors for small vessel disease (n = 5). These conditions may explain the preexisting lesions, but they were not the cause of the index stroke: A diagnosis of combined etiologies (e. g. small vessel disease plus LAA) according to TOAST-criteria would have been incorrect, because none of these patients had lacunar syndromes. Furthermore, aortic arch atherosclerosis < 4 mm without thrombotic apposition was not considered relevant in the presence of high-grade ICA-stenosis.

Multiple DWI-lesions with low ADC in a single vascular territory, without borderzone involvement (i. e. pattern 3), was associated with LAA-stroke, which was in line with earlier DWI-studies [8, 9, 15]. These findings may indicate that in LAA-stroke, emboli originating from an atherosclerotic plaque hit a single vascular territory (pattern 3), while in CE-stroke different circulations are involved (pattern 6). The fact that these differences are only significant if acute lesions are considered (i. e., DWI lesions with low ADC-signal) indicates the importance of ADC maps in determining stroke etiology.

Hyperintense DWI lesions in borderzone areas were associated with LAA. However, if only hyperintense DWI lesions with low ADC (i. e. acute lesions) were considered, borderzone involvement missed statistical significance. Previous DWI studies produced contradictory results in favor [13] as well as against [9] an association of borderzone infarction with ICA-stenosis, but none of them took into account the lesion signal on ADC maps. DWI lesions in borderzone areas occurring prior to the index stroke might account for these conflicting findings.

The distribution of lesion patterns in a subgroup of 26 patients with posterior circulation stroke syndromes (POCS) was similar in part A (analysis of all hyperin-

tense DWI lesions) and part B (analysis of hyperintense DWI lesions with low ADC): In parts A and B, pattern 3 was found in 5 LAA-patients and 2 CE-patients; pattern 6 occurred in 3 CE-patients (part A) and 2 CE-patients (part B), respectively, but never in LAA-stroke.

In our study, DWI failed to show cerebral ischemia in 6 % (i. e., 1 patient with LAA and 4 patients with CE), despite symptoms lasting > 24 hours. In these patients, DWI took place 9–54 hours after stroke onset. In 3 out of these DWI-negative stroke patients, the clinical syndrome pointed to a small brain stem lesion. The other two patients experienced a complete regression of symptoms later than 24 hours after stroke onset. Overall, our sensitivity of 94 % for visualization of acute infarction by DWI is in line with previously published data [16]. A post hoc analysis excluding patients with DWI-negative strokes did not substantially alter our results. The number of hyperintense DWI lesions remained significantly higher in LAA-stroke ($p = 0.028$), although the difference in DWI lesions with low ADC missed statistical significance ($p = 0.08$, data not shown in tables).

Lesion number and lesion multiplicity differ between stroke caused by large artery atherosclerosis and cardioembolic stroke. It is evident that these differences are not large enough to predict the stroke etiology in an individual patient. On the other hand, some of the observed lesion patterns (i. e., patterns 3 and 6) did indeed show such a strong association with stroke etiology. The presence of such a pattern may influence the choice of the next investigation (i. e. doppler/duplex-sonography or cardiac evaluation) in order to accelerate the diagnostic process. However, this is yet to be confirmed in a prospective study. An immediate implication of our findings results from the impact of the ADC-signal on lesion patterns. Preexisting hyperintense DWI-lesions in acute stroke may lead to the allocation of an "incorrect" lesion pattern and thereby assumption of an incorrect etiology, unless they are identified on corresponding ADC-maps.

Our study has the following limitations: (1) Owing to the retrospective design, the time interval between stroke onset and DWI varied within a time range, in which the apparent diffusion coefficient is known to change. However, the maximum interval of one week was chosen in analogy to several other studies [2, 9, 11, 19]. Furthermore, DWI has recently been shown to be clinically useful not just within the first few hours but up to weeks after ischemic stroke [10]. More importantly, the association between stroke etiology and number of ischemic lesions remained significant after correction for the interval between stroke onset and DWI. (2) The sample size of our study limits the possibility of subgroup analyses, e. g. with respect to certain stroke syndromes. Still, our sample size is comparable with the combined number of LAA-patients and CE-patients in a recent DWI-study including all stroke etiologies [8]. (3) We assessed the maximum diameter of the largest DWI lesion in each patient but did not calculate the total lesion volume. Therefore, the volumetric lesion load could not be compared between LAA and CE. However, a similar approach was used in other DWI-studies assessing lesion patterns [8, 19].

In conclusion, our study showed that multiple ischemic lesions occur more often in LAA-stroke than in CE-stroke. Different patterns of lesion distribution can be assigned to either of these etiologies. However, ADC maps should be used to identify subacute or chronic DWI lesions that may have occurred prior to the index event.

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